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THE PROBLEM OF DISSEMINATED SCLEROSIS.[1]

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UNTIL recently, no neurological disease had received so much attention from clinician, pathologist and bacteriologist as the one chosen for this Address. Despite this volume of work, the true nature of disseminated sclerosis still eludes us. With the prospect of an early return to peace-time conditions in clinical and bacteriological research, it appears to be a matter of some importance that this subject should once again be reviewed in the hope that fresh interest may be aroused in a problem which, on humanitarian grounds alone, deserves the attention of those best qualified to take part in its investigation.

The Pathological and Experimental Approach.

Our present-day conception of the histology of disseminated sclerosis dates from the work of Siemerling and Raecke (1914) and of Dawson (1916). We recognize from their descriptions of the disease that such terms as "disseminated sclerosis" and "sclerose en plaques" are inadequate since they fail to convey either the essential nature of the disease or the site of the initial lesion. Time will only permit of a brief reference to two aspects of their work which are of special interest to us at the present time. They commented on the remarkable symmetry of the plaques in the brain, especially those around the ventricles. Dawson could only explain this distribution on a vascular basis. He found that the patches of the disease appear within but do not coincide with the area of distribution of arteries. Vasodilatation is common, but according to Dawson neither thrombosis nor hæmorrhage are characteristic features. Only on the question of hæmorrhages did Siemerling and Raecke differ from this

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view. Of historical interest is a small book published in London in 1895 bearing the title "On the relation of Diseases of the Spinal Cord to the Distribution and Lesions of the Spinal Blood Vessels." The author was J. W. Williamson of Manchester and later, in a pathological paper on disseminated sclerosis, he elaborated this thesis (1903).

Dawson anticipated by nearly thirty years the modern conception of the demyelinating diseases. He considered that toxi-infective agents may produce a variety of changes in nervous tissue according to the nature of the noxa. These might range from simple degeneration of the tissue without inflammatory vascular changes to actual inflammation leading to necrosis. To quote his own words, "It is possible to go a stage further and assume that the toxin is so concentrated and acts so rapidly that it attacks not only the myelin sheath, but destroys the axis cylinder and then the meshes of the glia." With regard to the ætiology of the disease Dawson, after considering various possibilities, concluded that disseminated sclerosis is due to a specific morbid agent, probably a soluble toxin, which is conveyed to the nervous system by the blood channel, and that the occurrence of remissions and relapses necessitates the assumption of the latent presence of the morbid agent in the body.

No worker in this field has produced evidence which contradicts the important conclusions reached by Siemerling and Raecke and by Dawson that disseminated sclerosis is a form of acute or subacute disseminated encephalomyelitis due to a blood-borne infection. Brain, in a critical review published in 1930, discussed the various attempts made during the first part of this century to isolate a specific organism from the nervous system of fatal cases and to transmit the disease to animals. He showed that these attempts had either failed or had been inconclusive. More recently, Schaltenbrand (1940), working in Germany, has succeeded in producing a demyelinating disease in monkeys but has expressed doubt about the validity of his results on account of the occurrence of a spontaneous form of encephalomyelitis in these animals. His attempts to infect a small number of chronic psychotic patients met with no success. The negative results of much of the experimental work on disseminated sclerosis have renewed doubts about its infective nature and have led to a variety of experimental work on demyelination in the hope that more might be learned of the underlying process. Within the past fifteen years American opinion has been influenced by the work of Putnam and his associates (1935) who produced areas of demyelination in dogs by first blocking and then injecting the superior longitudinal sinus. They stated that the lesions resembled those of disseminated sclerosis. In a

later paper (1937) Putnam described venous thrombosis in nine out of seventeen cases of the disease. From these results and from his experimental work he has concluded that venous thrombosis is the essential histological lesion. Dawson's views on this subject have already been quoted. Recently Dow and Bergland (1942), in a careful examination of sixty plaques from five cases, found no evidence of thrombosis. Hurst (1944) in a recent review refers to experimental work including that of Hurst and Cooke (1942) in which blocking of capillaries led to demyelination. He concluded: "We cannot doubt, therefore, that demyelination with degeneration of axis cylinders may be a sequel to a relatively minor obstruction of the circulation in the white matter, an obstruction insufficiently important to lead to complete necrosis." Greenfield and King (1936) have criticized Putnam's histological data on technical grounds, and it would appear doubtful whether the results of his experimental work can be applied to the problem of disseminated sclerosis. It is difficult to visualize thrombosis as the primary lesion in view of the clinical fact that the duration of symptoms may, on occasions, be exceedingly brief. But, on the other hand, the abrupt onset of weakness in the lower limbs which may lead to a fall as well as the effect of emotion in other cases, suggest that a vascular mechanism may sometimes come into play.

In Hurst's review of this subject, reference is made to other methods by which demyelination may be brought about; a brief reference to this experimental work must suffice. Hurst and his co-workers (1942) produced lesions in the brains of monkeys by intramuscular injections of potassium cyanide. The changes in the brain varied both in situation and character according to the dose given. If a massive fatal dose was administered necrotic lesions occurred mainly in the cerebral and cerebellar cortex. If, on the other hand, sublethal doses were given at intervals the maximal changes were found in the white matter including the optic tracts, whilst the cortex was spared, a distribution which Hurst points out is very similar to that in Schilder's disease. Finally, if small doses were repeatedly given over a long period of time, the grey matter of the basal ganglia usually escaped, but progressive demyelination with loss of axis cylinders followed. With sodium azide much the same results were obtained including an abrupt onset of blindness and other symptoms after repeated small doses. No biochemical explanation for this demyelination could be demonstrated. Hurst concluded that the basis of this change in the brain was a histotoxic anoxia, i.e an alteration in the cellular enzyme system, whereby oxygen, although present in sufficient quantities in the blood, could not be utilized. Morrison (1946) in a recent study of the

effects of exposing monkeys to atmospheres of low oxygen concentration produced results strikingly similar to those of Hurst, especially in the varying histological picture which followed a greater or lesser degree of anoxia.

The application of this work to the problem of disseminated sclerosis is only an indirect one, but it underlines two important facts; first, that similar histological changes may be produced by a number of different agents, and secondly that the localization of the lesions and the type of tissue reaction varies according to the intensity or dosage of the noxa. Twenty years ago the presence of lymphocytes and plasma cells in the perivascular spaces of acute cases of disseminated sclerosis could be used as an argument in favour of the infective nature of the disease, but we now know that such elements may appear in response to lack of oxygen, poisons, &c., or to the tissue changes induced by such means. Nevertheless, the results of this recent work on demyelination do not warrant a departure from the view that the form of subacute disseminated encephalomyelitis which we recognize as disseminated sclerosis can be other than toxi-infective in origin.

There remain for discussion two further lines of approach which are inter-related, first, the view that allergy may be a factor in disseminated sclerosis, and secondly that the disease may be caused by a bacterial agent or by a filter-passing virus. It will be recalled that in 1913 McIntosh and Fildes explained the phenomena of parasyphilis on the basis of "hyperallergie," a term used by von Pirquet in 1907 to explain the local reaction in the arm and the occurrence of fever after vaccination. This theory has been applied to the form of encephalomyelitis that may follow vaccination and certain of the infectious fevers (Van Bogaert, 1932, and Finley, 1938). Ferraro (1944) in a recent review of this subject concludes that unification of the pathology of the demyelinating diseases seems possible if they are considered as an expression of an allergic reaction in nervous tissue. He further suggests that in disseminated sclerosis, once the initial lesion has been established in the brain, other factors may play a role in the progress of the disease or in its phase of activation. There would appear to be two possible variations to this view; first, that the agent in disseminated sclerosis is the same throughout, and that it acts "à distance," or secondly that, by analogy with syphilis, the infective agent initially invades the nervous system and there remains latent for a varying period. There are certain features of disseminated sclerosis, notably the relapsing nature of the disease, that could be explained on the basis of allergy, but at the present time further speculation on this point would serve no useful purpose.

As already stated, the efforts made by the experimental bacteriologist to establish the nature of the causal agent have, up to the present time, failed. There is no evidence to suggest that an abnormal organism is present in the alimentary tract of these patients or that any of the known bacteria or their toxins can reproduce the clinical and histological picture of disseminated sclerosis, although it is known that certain of them may cause demyelination. Therefore, while we should reserve final judgment on the possible role of a toxin these negative findings would seem to point to a filter-passing virus rather than to a bacterial agent. Support for this view is provided by the results of recent work carried out in Moscow by Margulis, Soloviev and Shubladze (1946). I am indebted to Dr. Carmichael for an opportunity of reading their paper prior to its publication in the current number of the *Journal of Neurology, Psychiatry and Neuro-surgery*. They have obtained identical strains of virus from two cases of acute disseminated encephalomyelitis. In the first of these cases the disease followed a relapsing course between 1942 and 1945, the patient making a good recovery from each relapse; whilst in the second case death occurred within seven days. By means of strains from these two cases Margulis and his co-workers succeeded in producing acute disseminated encephalomyelitis in animals such as rabbits and dogs. In a series of neutralization tests they found that 80 per cent. of patients who had recovered from acute disseminated encephalomyelitis gave positive results, whilst in 50 per cent. of a small series of cases of disseminated sclerosis the tests were also positive. Finally, they inoculated virus into the sciatic nerve of rabbits and they proved that within twenty-four hours it had reached the brain. This suggested a hæmatogenous spread, although changes were also found in the lumbar cord which they attributed to a slower ascending infection along the sciatic nerve. The authors state that this work represents the first successful attempt to isolate a virus from a human case of acute disseminated encephalomyelitis and to reproduce the disease in animals.

On previous occasions claims have been put forward in connection with disseminated sclerosis that have not stood the test of time. On account of the importance of their results it is hoped that this work will be repeated at an early date in more than one laboratory in this country. Meanwhile, we shall await with real interest the further results of this work which is still proceeding.

If we assume that disseminated sclerosis is toxi-infective in origin, there remains for consideration the mode of infection. We know that a bacterial agent or its toxin can reach the nervous system in one of three

ways, by the blood-stream, by nervous pathways and lastly by direct extension from a neighbouring focus, usually in bone. In disseminated sclerosis the last possibility needs no further consideration. It will be recalled that at the beginning of this century the attention of clinicians and experimental pathologists in France, Germany and this country was focused on the peripheral nervous system as a route of infection by the sequence of events that occurred in rabies, tetanus and diphtheria. In this country Orr and Rows (1914) showed that bacteria, when placed in or around a peripheral nerve such as the sciatic, produced an inflammatory reaction of the spinal roots and cord meninges followed by degenerative changes in the spinal cord or brain-stem at a level which corresponded with the nerve supply of the infected focus. The intensity of these changes depended on whether bacteria or their toxin reached the cord. Furthermore, Orr, Rows and Stephenson (1913) described a number of clinical cases of prolonged suppuration in which degenerative changes were found in the spinal cord. The general view was held that, as in tetanus and diphtheria, the bacteria or their toxin reached the spinal cord by the perineural lymphatics. More recently the experimental work of Fairbrother and Hurst (1930) on poliomyelitis in monkeys suggested that in these animals the virus travelled via axis cylinders.

In an important series of papers published between 1934 and 1938 Abel and his associates criticized the existing theories as to the neural spread of tetanus toxin, and from their experimental data concluded that the toxin is carried to the nervous system by the blood and lymph vascular systems. They explained local tetanus by the direct action of the toxin on neighbouring muscles. This view has received confirmation from the work of Baker (1942) who examined the central nervous system in 12 fatal cases of tetanus. In cases dying within two or three days the initial changes were found in the nerve cells of the brain. From the fifth to the twelfth days perivascular demyelination was apparent throughout both grey and white matter. The glial changes were the last to appear.

In diphtheria whether of the fauces or of the skin, a hæmatogenous and neural spread of toxin may take place. In certain forms of encephalitis in man, notably Japanese encephalitis, equine encephalomyelitis, the recently described Far Eastern tick-borne spring/summer encephalitis (Sieber and Soloviev, 1946) and the meningo-encephalitis that may accompany tick-borne relapsing fever, infection takes place by the skin through the agency of a vector. A case of encephalomyelitis reported from Northern Australia by Horan and others (1944) further illustrates this point. Early in December, 1942, Private S. was admitted

to hospital with acute polyarthritis. Just prior to admission he had suffered from an infected laceration of the left 5th finger. Tenderness along the course of the left ulnar nerve was noted during his stay in hospital. The arthritis cleared up. Early in February, 1943, whilst at a convalescent home, he complained of pain in the middle of the left arm and developed headache. In hospital paresis and sensory loss in the left arm developed, followed by signs of meningitis. The cerebrospinal fluid showed a well-marked pleocytosis, but cultures were negative. In the last five days of life paræsthesiæ and slight weakness in the left leg and foot, numbness in the left side of the chest, paresis of the lower cranial nerves and respiratory embarrassment were noted. Histological examination showed sharply defined areas of focal necrosis and a diffuse cellular infiltration of adjacent areas of nerve tissue. The authors considered that the pathogenic agent entered by the skin and travelled by nervous pathways to the spinal cord, and from there to the brain-stem and cerebellum and that the mode of spread suggested a virus infection.

If this case of encephalomyelitis be accepted as an example of infection entering the nervous system via the skin, then a latent interval of two months existed between the date of the original lesion and the appearance of neurological signs and in this respect the case bears comparison with rabies. Thus there is good evidence in support of the view that from a focus in the skin bacteria and their toxins or a virus may reach the nervous system either by neural pathways or by the blood-stream, the precise distribution of the lesions depending on the neurotropic tendencies of the particular agent.

Turning to the alimentary tract as a portal of entry, we find ourselves on less solid ground. However, in faucial diphtheria there is evidence of both local and hæmatogenous spread of toxin. In bulbar poliomyelitis following tonsillectomy the evidence of local neural spread seems strong. The possibility that the virus of poliomyelitis may reach the spinal cord from the alimentary tract via the sympathetic nervous system has been considered by Toomey (1935). It will be recalled that Orr and Rows (1918) put forward the hypothesis that a disturbance of the thoracicolumbar sympathetic system might be responsible for the localization of the degenerated areas in the spinal cord which followed the placing of infected celloidin capsules in the abdomen of rabbits. They envisaged a disturbance of the sympathetic by pathological stimuli which caused dilatation of pial vessels thereby increasing their permeability. It is of interest to note that within the past ten years a similar theory has been the basis of a series of experiments carried out in France by Reilly.

Laporte and others (1942) on the role of the sympathetic in renal pathology. Although no further reference will be made to the sympathetic nervous system, its possible significance when considering certain aspects of the problem of disseminated sclerosis should be borne in mind.

The Clinical Approach.

The clinical approach to the problem of disseminated sclerosis will be limited to a brief consideration of those features of the disease which seem to throw some light on its causation. In addition, the results of a social and medical survey in a series of cases will be given. Unlike the majority of organic nervous diseases, disseminated sclerosis is distinguished by the remarkable variations in its clinical course. Remissions may last for more than ten years or for less than six months. Furthermore, the degree of recovery may vary within wide limits. For example, the disease may appear in a florid form but, despite the multiplicity of signs, a good clinical recovery and a lengthy remission may follow. By contrast mild symptoms may recur every few months over a period of several years and yet the stage of chronic paraplegia may be long deferred. Age modifies the course of the disease; the older the patient the more localized are the signs and the more chronic the course. When the disease first attacks an individual in the fifth decade of life, remissions are as a rule inconspicuous, the disease tending to run a slowly progressive course interrupted by short periods of arrest. Retrobulbar neuritis and euphoria are uncommon in such cases and the cerebrospinal fluid is normal more frequently than in the average case. On the other hand, the florid form of the disease is seldom seen outside the younger age-groups. In the past these characteristic features of disseminated sclerosis have been interpreted in terms of the disease rather than of the individual affected by it. Despite its protean nature clinician and pathologist have recognized the disease as a clinical entity although realizing that the term disseminated sclerosis may cover more than one type of encephalomyelitis. But at the present stage of our knowledge it seems justifiable to postulate only one causal agent. Therefore, the peculiar course of the disease can be explained either in terms of the patient or of the agent. Since we have no precise knowledge of the character of the agent we may for the moment assume that the individual's reaction to the disease is the prime factor in modifying its course. From our knowledge of infections in general it can be inferred that the clinical features of disseminated sclerosis are in all probability the result of an immune reaction to an infection which

varies not only from case to case but also during the course of each patient's illness. In conjunction with the abnormal findings in the cerebrospinal fluid this view lends further support to the theory of an infection. If it is assumed that this infection is due to a virus we must be prepared to broaden our view of the symptomatology of the disease so as to recognize not only an acute stage, but also the existence of subclinical forms, a view also held by Schaltenbrand.

Brief reference must be made to the relationship of acute disseminated encephalomyelitis to disseminated sclerosis. We are familiar with cases of encephalomyelitis which begin abruptly after a so-called "influenzal" attack. The clinical picture may be compatible with a diagnosis of disseminated sclerosis, but in other cases atypical features are present suggesting the possibility of acute disseminated encephalomyelitis. It will be recalled that between 1925 and 1930 small outbreaks of this condition were reported from Europe and in this country. Different opinions were held as to its relationship to disseminated sclerosis, the majority favouring the view that the two conditions were essentially identical.

I have recently followed up two out of four cases reported in 1930 as examples of acute disseminated encephalomyelitis (1931), and in addition a third case in which a similar diagnosis was made in 1931. Each of these cases has since relapsed on more than one occasion, one of them terminating fatally in 1941. The fact that these cases relapsed does not necessarily negative the original diagnosis. Before assuming the complete identity of these two forms of encephalomyelitis, we should recognize that the boundaries of disseminated sclerosis are ill-defined and that they will remain so until the cause of this disease is made known to us.

A number of observers, notably Allison (1931) and Von Hoesslin (1934), have made surveys in this disease with the purpose of discovering any facts which might throw light on its causation. The results of such surveys, in the main, confirm the occasional role of trauma, pregnancy and other factors in precipitating the disease.

Despite the obvious limitations of this method of approach, it was felt that by a careful enquiry into the past history of these patients it might be possible to find at least a partial answer to the question "Why does disseminated sclerosis typically attack young persons who are in good health?" In 1937 a detailed method of history-taking in cases of disseminated sclerosis was begun by the writer, but owing to the war this work was interrupted and has only been resumed during the past year. Although the number of cases, namely 142, is too small to be of statistical value, certain facts seem to emerge which may not be without interest.

Eighteen cases have been omitted from the following table because the period of observation was not sufficiently long to determine the course of the disease.

TABLE SHOWING AGE AT ONSET AND SEX INCIDENCE IN RELATION TO THE TWO COMMON TYPES OF DISSEMINATED SCLEROSIS IN 124 CASES.

	Relapsing		*Ch. Progressive*		
Age-group	*M.*	*F.*	*M.*	*F.*	*Total*
10–20 years ..	8	10	—	—	14·5%
20–30 years ..	18	32	—	—	40%
30–40 years ..	12	19	3	4	31%
40–50 years ..	1	6	3	6	13%
50–60 years ..	—	—	—	2	1·5%
Number of cases	39	67	6	12	

Miscellaneous facts.—In this country it is generally held that the disease is more common in females and the present series though small in numbers bears out this point, more particularly in regard to cases in the fifth decade. In other European countries and in America, either males predominate or there is no significant sex distribution. The disease shows no social discrimination and occupation appears to play no part in its causation. Both town dwellers and rural workers may be affected. An analysis of the onset of the disease according to each quarter of the year was made: the figures did not suggest a seasonal incidence in this country. Although geographical distribution did not come within the scope of this enquiry some reference to it must be made. The disease is relatively common in northern European countries, whereas in Africa, India and the Far East it is rare, and in Australia definitely less common than in this country (Hurst, 1941). Although large forces of British troops were employed in the Middle East and India during the war, those of us who worked in these countries were struck by the rarity of this disease among these troops, despite the fact that, for the most part, they came from the age-groups which show the highest incidence of disseminated sclerosis. The disease is exceedingly rare amongst Indians, and no case came to my notice in which this diagnosis seemed probable. There is as yet no explanation of these facts, nor of its occasional occurrence in small foci, but if the disease is regarded as an infection then such variations in its distribution become more easily understood.

Familial incidence.—The number of authenticated cases of familial disseminated sclerosis is not large, but there can be no doubt that the disease may attack more than one member of a family. Curtius (1933) examined 1,036 relatives of 56 families in which a case of disseminated sclerosis had occurred; in six of these families more than one case was

found. It is necessary to scrutinize with care the diagnosis of disseminated sclerosis in suspected familial cases so as to exclude hereditary cases of cerebello-pyramidal disease such as those described by Ferguson and Critchley (1929). With these reservations in mind I am satisfied that in 8 out of a total of 142 cases (5 per cent.) there was a familial incidence. In 6 cases the disease affected siblings; in one case the father and in the remaining case the mother of the patient was affected. The familial incidence would seem to indicate an occasional hereditary predisposition to the disease, and in this respect disseminated sclerosis might be compared with tuberculosis.

Type of individual.—Are there any particular physical or mental characteristics that render an individual susceptible to the disease? The necessary data for a survey of this nature are considerable and in the present instance they fell far short of the required standard. However, it can be said that there appeared to be no distinctive type of body build or colouring, though obesity would seem to give some protection against the disease. The incidence of mild anxiety states appeared to be no greater than in the general population. The occasional relationship between psychic trauma and the onset or course of the disease is well recognized: in several patients in this series there seemed little doubt that a psychogenic factor unmasked the disease. The following two cases illustrate this point:

Mrs. C., aged 25, previously a trained nurse, had been subject since childhood to urticaria and diarrhœa when under mental stress. Since the age of 15 she has had four attacks of retrobulbar neuritis, each occasion coinciding with a period of tension, such as examination, or on the last occasion the return of her husband from overseas. In addition to pallor of the discs this patient now shows early pyramidal signs.

N. W. J., in April, 1934, when aged 21, sustained a through and through wound of the right foot as a result of jumping on a nail. The wound was dressed and he stayed away from work for two weeks. In July of the same year, while riding his motorcycle with his fiancée on the pillion seat, he rounded a corner at an excessive speed and had a narrow escape from a head-on collision with a car. At once his legs felt numb: "As if the blood had drained from them." He proceeded on his way but for the next ten minutes he had considerable difficulty in keeping his feet on the foot-rests. Within an hour the legs felt normal. He attributed the loss of feeling in his legs to the mental shock which he experienced. Seven days later his legs felt tired and numb and he tended to drag the right one. These symptoms lasted several weeks and then passed off. In January, 1938, he fell down some stairs and then noticed pins and needles in both legs, and a dead feeling over the abdomen and lower chest. When examined in April, 1938, he showed nystagmus, impaired postural sense in the fingers of the right hand and a mild spastic paraplegia. Thereafter the disease followed a typically relapsing course until 1944 since when he has been bedridden.

In both of these cases it might be supposed that an abnormal degree

of sympathetic stimulation caused a vascular disturbance in the central nervous system resulting in the appearance of clinical signs. However, if this inference is correct, it only indicates in a general way the mechanism by which symptoms may be produced in individual cases. The first of these two cases leads us to consider the incidence of generalized allergy in disseminated sclerosis. In the present series approximately 6 per cent. of the patients gave a history of asthma, hay fever or urticaria. Baer and Sulzberger (1939) investigated 30 cases of disseminated sclerosis from this point of view. In 10 cases there was a personal or familial allergic history, or the patient gave positive skin tests. They concluded that these results corresponded with high average values. In the present series migraine alone was not accepted as evidence of allergy; in about a quarter of the cases a positive history was obtained prior to the onset of the disease. In view of the frequency of this condition amongst the present-day population it is doubtful whether any significance can be attached to this finding.

General health, weight and food in relation to onset.—Approximately 20 per cent. of patients stated that they felt "run down" before the illness began. Comparison of the approximate weight at onset with previous average weight was made in 90 cases. In 28 cases the weight was below the average, but with few exceptions the loss probably did not exceed a few pounds. No detailed dietetic survey was attempted, but in 71 cases an approximate idea of diet was obtained by enquiring into the regularity and number of meals, type of food taken, and approximate amounts at each meal. In 10 cases meals were irregular or appeared to have been deficient in quantity. In no case was there evidence of malnutrition. Brickner and Brill (1941) carried out a dietetic enquiry in 34 cases of disseminated sclerosis. In only 4 cases was the diet definitely deficient, although the majority of patients were poor eaters. Thus in the absence of any real evidence to the contrary, it may be assumed that a food deficiency is not important in this disease.

The impression gained from this part of the enquiry was that, as a rule, the individual when first attacked by disseminated sclerosis is in good general health, but that in a minority a subnormal state of health, undernourishment or loss of weight may have lowered resistance.

Trauma.—Certain writers, notably Von Hoesslin, have stressed trauma as a precipitating factor. In his series of 516 cases the onset of the disease closely followed trauma in 11·4 per cent. In the present series trauma, unassociated with sepsis and unrelated to a fall caused by the disease, occurred within a month of the onset in only 8 cases (5 per cent.). In two cases the onset of the symptoms appeared within a few hours of the bursting of

a bomb at close quarters; in neither of these cases could the possibility of a minor degree of blast be excluded. Von Hoesslin has reported cases in which an injury to a limb was followed by the first signs of the disease in that limb. In two cases of the present series retrobulbar neuritis occurred as the initial symptom within twenty-four and seventy-two hours respectively of a minor trauma to the same eye. After excluding those cases in which the disease itself was responsible for the alleged trauma, there remain a few cases of disseminated sclerosis in which there can be little doubt of the close relationship between peripheral trauma and the appearance of signs. A further study of such cases is called for since they would seem to indicate the possibility of abnormal reflex or sympathetic activity in the cord in response to peripheral trauma.

Evidence of infection preceding onset.—Bearing in mind the probability that disseminated sclerosis is due to a toxi-infection, it was necessary to ascertain the incidence of fever and constitutional symptoms occurring within a month of the onset. In only 8 cases (5 per cent.) was there a history of fever associated with a chill, generalized pains or sore throat, usually described as "influenza." In 4 other cases a cold or sore throat without evidence of fever was obtained. In no case did the disease follow one of the infectious fevers. Barker (1922) estimated that in only 3 per cent. of cases was there a history of an acute infection within three months of the onset. In view of these essentially negative findings, the scope of the enquiry was extended to include any incidents in the past history of these patients that might give some indication as to the route by which the agent could have reached the nervous system. It may be stated that with the exception of certain cases of peripheral sepsis and a small group of cases beginning with influenza, the result of this enquiry was mainly negative. The following cases illustrate a sequence of events that may not be without significance:—

Case 1.—Recurrent abscess left side of neck followed by pain left arm lasting nine months. Normal health for one year. Return of pain left arm and appearance of signs of disseminated sclerosis.

R. J. M., when aged 24, on March 20, 1939, noticed a small septic spot on the left side of his neck. A week later a boil developed which discharged. On April 1 a large fluctuating swelling was present on the left side of the neck and he was admitted to hospital. The condition subsided but early in July he noticed that the glands in the left side of the neck were still swollen and that he had an aching pain in the left shoulder. By August adenitis had recurred and he was again admitted to hospital where a cervical abscess was incised and drained. The wound healed but the pain in the shoulder persisted and spread down the outer aspect of the upper arm. When re-examined in October of the same year no cause for the pain could be found. In 1940 he was called up for military service and was able to do route marches of 20 miles. However, in January, 1941, he was admitted

to the West London Hospital under the care of Dr. R. Ironside, to whom I am indebted for the following notes. The patient complained of pain in the left shoulder and elbow, difficulty in writing and unsteadiness in walking. He showed the following positive signs: nystagmus, slurred speech, intention tremor in the upper limbs and an ataxic gait. A diagnosis of disseminated sclerosis was made. In July, 1941, he was discharged from the Army with that diagnosis. In March, 1946, he showed a typical picture of the advanced stage of the disease. The superficial and deep cervical glands of the left side were still enlarged.

Case 2.—Traumatic cellulitis left arm with adenitis. Twelve months later paræsthesiæ left arm followed by diplopia. Subsequently typical picture of disseminated sclerosis.

R. V. W., when aged 22, in August, 1933, trapped his left thumb in the gate of an automatic lift. Several days later the thumb became painful and swollen. The inflammation spread from the thumb to the arm which showed a red streak running up it. There was intense pain in the arm and armpit. The condition lasted several weeks but finally subsided. In July of the following year, after a strenuous cycle ride on a hot day, he experienced such intense itching in the left arm that he had difficulty in sleeping that night. Within forty-eight hours the fingers of his left hand became as it were "glued together." A few days later while undergoing treatment for "neuritis" of the arm he suddenly lost his balance and fell off a chair. He regained the full use of the arm, but in the following month he had double vision which lasted three or four hours. In other respects his general health was good. In May, 1935, double vision returned for two months. The patient subsequently developed a weakness of the left foot. In 1940 he was seen by Professor P. C. Cloake and I am indebted to him for notes on his condition which showed that he had rotatory nystagmus, diplopia due to paresis of the left inferior rectus muscle, intention tremor and a doubtful extensor plantar response. A diagnosis of disseminated sclerosis was made. In April, 1941, both legs became weak and numb and the plantar response by then had become doubly extensor. By 1946 the patient had become severely paraplegic.

In neither of these cases was there any clinical evidence of disseminated sclerosis prior to the severe infection in the neck and arm respectively. In both cases there were local signs consisting of intermittent pain in the arm in the first case and paræsthesiæ in the second case. The interval between the height of infection and the first sign of disseminated sclerosis was 18 and 12 months respectively. The evidence that in these two cases a peripheral focus of infection and disseminated sclerosis were related is purely circumstantial.

The first of these patients recalls a case reported by Orr and Rows in 1906 in which a brachial neuritis was associated with a deep-seated abscess involving the brachial plexus and root ganglia on the same side. Death occurred on the twelfth day. Cocci were present in the root ganglia but no inflammatory changes were seen in the dura or pia-arachnoid. An acute degeneration was found in the cervical region of the cord, particularly in the intra-medullary portion of the corresponding posterior roots and on either side of the postero-median fissure.

If the possibility be accepted that in the cases I have described the agent responsible for disseminated sclerosis may have reached the nervous system via the skin, then it may be assumed that it did so during the stage of active infection. Further, it must be supposed that a latent interval can exist between this invasion and the appearance of signs. From this premise two further possibilities present themselves. First, that the original focus in the skin may be comparatively slight and secondly that if months may elapse before signs of disseminated sclerosis declare themselves, then the interval may be much longer. This last point suggests that sensitization of the nervous system may take place at the time of the original infection and the analogy often made between disseminated sclerosis and neurosyphilis becomes a closer one.

The following case illustrates a milder type of initial lesion:—

Case 3.—Operation for bursitis left foot followed by pain, swelling and weakness of left leg. Two years later unsteadiness in walking and subsequently typical signs of disseminated sclerosis.

O. W., a female, when aged 20, was operated upon at the Middlesex Hospital in April, 1933, for an inflamed bursa of the left foot. Section of the bursa showed chronic inflammatory changes. The wound broke down and discharged; healing did not take place for about a month. From that time onwards there was intermittent swelling of the left ankle. The patient noticed that the ankle was at times painful and that she was inclined "to go over" on it. By the autumn of 1933 the pain had gone and the swelling was slight, but the left ankle continued to be weak and if she walked a long way the left foot used to drag. In May, 1935, she noticed unsteadiness in walking and increased weakness of the left leg. In June, 1936, she was euphoric and showed pallor of the right disc, nystagmus, ataxia of both upper limbs and a left extensor plantar response. The cerebrospinal fluid was normal.

In the present series a positive history of peripheral sepsis within one year of the onset was only obtained in 18 cases (13 per cent.). In 9 of these cases the first sign of the disease occurred at approximately the same segmental level as that supplying the infective focus. Two objections to this theory at once suggest themselves. First, cutaneous sepsis is common and by comparison disseminated sclerosis is rare; and secondly, there was no evidence of an increased incidence of the disease following the first World War despite the thousands of men who had septic wounds. These facts would suggest that the known bacteria associated with suppuration may play no direct part in the causation of the disease, but the possibility of a secondary virus infection is not excluded. A relationship between retrobulbar neuritis and sinus infection is not borne out in this series. Of 25 cases (18 per cent.) in which retrobulbar neuritis was the sole initial symptom, only 2 cases gave a history suggesting recent or

old infection of the sinuses. It would seem probable that the frequency with which the optic nerves and chiasma are affected in certain of the demyelinating diseases may depend on neurotropic or other factors.

Since much that I have said on the possible role of the skin as a portal of entry in certain cases of disseminated sclerosis is speculative, no good purpose would be served by pursuing the subject further.

Conclusions.

The conclusions reached in this paper may be briefly summarized as follows. The cause of disseminated sclerosis remains unknown, but it would seem to lie either in the direction of a biochemical or enzyme abnormality, of which proof is so far lacking, or on the other hand a toxi-infective process. Our increasing knowledge of the various forms of encephalitis and encephalomyelitis in man and the lower animals, and the part played by viruses in certain of them when viewed against the histological background of disseminated sclerosis suggests that this disease is also infective in origin. The results of the clinical approach bring to light no facts which are contrary to this view and some which seem to favour it. The view is put forward that the course of the disease is determined by an immune reaction to an infection, and that the extent of this reaction varies considerably from case to case. The familial incidence of the disease is significant and suggests that an inherited constitutional factor may render an individual more susceptible to it. Pregnancy, trauma and mental stress may in individual cases precipitate the disease or may be closely associated with a relapse. These facts are not inconsistent with the theory of an infection but at the same time a further study of such cases is desirable in order to understand the manner in which symptoms are produced. With the exception of cases in which there are "influenzal" symptoms, the onset of the disease is not generally accompanied or preceded by constitutional symptoms. Thus the possibility arises that invasion of the nervous system and the appearance of the first sign of the disease may not always coincide in time but that the former may take place months or years previously as in rabies and syphilis. If this premise be admitted then the question arises at what point in the patient's life history did the nervous system become infected or sensitized? In the investigation of a series of 142 cases no single common factor could be found which provided an answer to this question, although the scope of the enquiry may not have been sufficiently wide. Attention was next turned to the portal of entry of the hypothetical agent or toxin, and by analogy with other infections of the nervous system, it was inferred that the skin and

the alimentary tract were the likeliest starting points of the invader. Furthermore, from our knowledge of the histology of disseminated sclerosis it was necessary to postulate a hæmatogenous spread from the focus with or without additional local spread by cranial or peripheral nerve pathways.

In a number of cases in this series the clinical onset of the disease was preceded at varying intervals by an infective focus of the skin or subcutaneous tissue. In certain of these cases local pain and swelling persisted suggesting the presence of a chronic inflammatory process. The fact that the first sign of disseminated sclerosis sometimes occurred at a segmental level roughly corresponding to the infected limb suggests that this sequence of events was no mere coincidence. It is fully realized that the evidence in favour of the skin as an occasional portal of entry in disseminated sclerosis is purely circumstantial, but it seems to warrant further consideration in view of the part played by the skin in other infections of the nervous system. On theoretical grounds the possibility of other foci of infection playing a similar role must be borne in mind. The remaining portal of entry to be considered is the alimentary tract. I have already referred to a small group of cases in which influenzal symptoms immediately preceded the onset of the disease, thus suggesting the throat as a point of entry. The fact that a history of intestinal disorder prior to the onset of the disease is rarely obtained in these patients should not exclude the intestinal tract from consideration in any further research. Finally, I wish to make it clear that in the majority of patients included in this investigation no clue could be obtained as to how the disease originated.

The proof of a virus infection whether by direct or indirect means would be of the greatest help to future progress in our knowledge of the disease and its treatment. I hope that the controversial nature of this Address may be justified if only by drawing attention to the increasing evidence in support of the infective nature of disseminated sclerosis and to the urgent need of carefully planned research work based on the close co-operation of clinician and bacteriologist.

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HEREDO-DEGENERATIVE HEMIBALLISMUS.

A Contribution to the Question of Primary Atrophy of the Corpus Luysii.

BY JEAN TITICA AND LUDO VAN BOGAERT.

DURING 1943 and 1944 we had under observation a patient, approaching 50 years of age, with a bizarre neuropsychological syndrome with which we were unfamiliar clinically. The condition was one of progressive dementia with hemiballismus. It was familial but without hereditary history, no evidence of vascular disease was present, and the pathological examination indicated that it belonged to the rare category of heredo-degenerative hemiballismus.

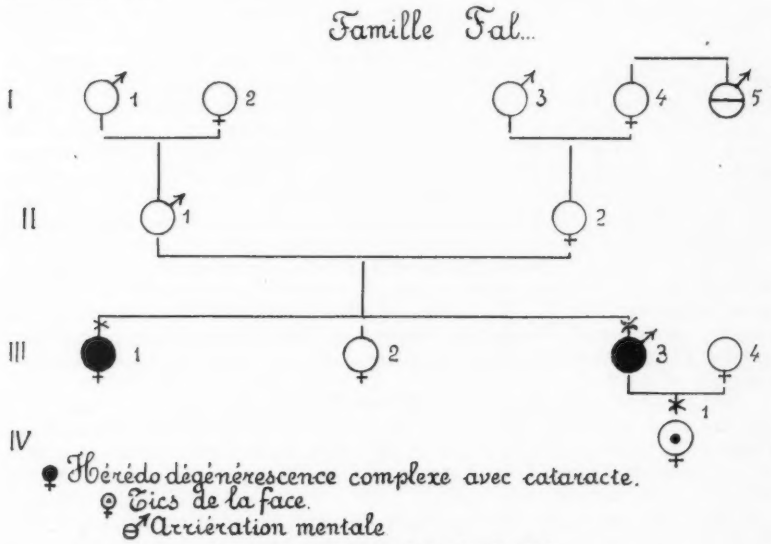

FIG. 1.—Genealogical tree of the family Fal . . .

CLINICAL EXAMINATION.

The patient, Fal . . ., was aged 47. He entered the Neuropsychiatric Centre at Brussels on May 27, 1943, and died on April 25, 1944.

Family history.—His father (II/1) at present 85 years old, has always been well; he had no siblings; his parents died at an advanced age without showing any evidence of neurological disease.

His mother (II/2) died at the age of 68 from "an ulcer of the pancreas." She also was an only child and her parents had not shown nervous symptoms. Her father was bronchitic. A brother of the maternal grandfather (I/5) was considered "simple-minded," but had always worked in the house and died at about 80 years of age.

The patient (Fal . . .) had two sisters, both older than himself. The younger (III/2) from whom we obtained our information about the family was 49. Although apparently well, she had had no children. The elder sister (III/1) died in March, 1944, at the age of 54 from a disease which began fourteen years before with cataract first in one eye, and two years later in the other. It was considered a special form of cataract by the ophthalmologist who operated on it. She then developed intention tremor, absent during sleep and rest, but becoming so violent during movement that the patient had great difficulty in carrying a glass of water to her mouth without spilling it. Since 1940, she had been unable to do her washing and her other household tasks. During the last two years of her life, progressive loss of equilibrium set in. She walked with a drunken gait and frequently fell; she had to hold the back of a chair to get about and finally became bedridden. During recent months, she had delusions, saying, for example, that her husband was dead. She also had periods of agitation in which she screamed without evident cause and protested that she could not stop herself. When such attacks occurred during the night she shut herself in the cellar so that she should not disturb the sleep of the household.

Personal history.—Fal . . . (III/3), a farmer, married in 1930. His wife (III/4) has had one daughter (IV/1) who is at present 13 years old and has a facial tic. Till 1940 he was always well. He occasionally drank too much and was easily upset by liquor. When he drank beer he got a violent headache. His family said that a short time before the war he had several falls in which he hurt his head, but none of these injuries was severe. He was greatly shaken by the events of May, 1940. During the evacuation he was for several hours in a bewildered condition and on his return to Belgium was never quite well again. From that time, he noticed the sight of his left eye becoming dim and this increased so rapidly that he soon lost the sight of it completely. Shortly after this, involuntary contorting movements of the left arm and grimacing set in and became progressively worse. He found increasing difficulty in walking and often fell to the left, and in 1941 he gave up his business. During the summer of 1942 he became insanely jealous, bullying his wife, and upbraiding her unreasonably. At times he was disorientated, especially at night.

State on admission in May, 1943.—He was then 47 years old. His general nutrition was poor, his weight 116 lb. His skin and conjunctiva were of normal colour. Temperature normal. There was no enlargement of the heart, the apex being in the 5th intercostal space in the mammary line and there was no evidence of aortic dilatation. No murmurs were heard. There was no disturbance of the peripheral circulation, and no thickening of palpable arteries. Pulse, 72 per minute, regular. Blood-pressure 130/80. His tongue was clean and moist; the abdomen not tender to palpation. The liver was diminished in size, its lower border being found on percussion two fingerbreadths above the costal margin. The examination of the other organs of the body showed no evident abnormality in them. Wassermann reaction was negative in the blood; blood urea 26 mgm. per 100 c.c. Lumbar puncture, in the recumbent position, gave a clear fluid at a pressure (on the Claude manometer) of 350 mm. before and 200 mm. after the removal of 8 c.c. of fluid. There was no spinal block to the Queckenstedt test. Examination of the fluid showed: 0·3 cells per c.mm., 40 mgm. protein per 100 c.c., Ravaut, Pandy and

Weichbrodt reactions negative, Wassermann reaction negative, Colloidal benzoin 11001,11000,00000.

Neurological examination showed grimacing movements and frequent involuntary movements of wide range in the left upper limb. Grimacing was almost constant, affecting both sides of the face, particularly round the mouth. The involuntary movements consisted in throwing the whole arm backwards and outwards, in turning the limb round its own axis and in movements of circumduction. They ceased during sleep and were slight when he lay in bed, increasing in frequency and range when he sat up in bed and still more when he stood erect. They were especially severe when he tried to move, and on such occasions similar movements of smaller range sometimes appeared in his right arm.

Voluntary movements of the face were intact. His speech was slow and thick with much stammering, and was scarcely intelligible. He could use his right arm without tremor or dysmetria. He walked on a wide base. There was considerable hypotonia of all the musculature except in the left upper limb which, on the contrary, was hypertonic. All the deep reflexes were symmetrical and of normal facility, knee and ankle clonus were absent, and the plantar responses were of flexor type. Cutaneous sensibility was normal. There was no tenderness of muscles or nerve trunks.

The pupils were equal and regular and reacted normally. There was no nystagmus or disturbance of external ocular movements. A well-advanced cataract was present in the left eye and early one in the right eye.

The *mental state* varied from one moment to the next. Sometimes he seemed quite lucid and calm; at other times agitated and confused. Although rather deaf, he answered readily questions which were put to him. He gave his age at once, but hesitated when asked the exact date of his birth. He knew the date and how long he had been in hospital, which he thought he had entered for the cure of his cataract. He gave vent without any reserve to ideas of persecution in the form of jealousy, saying that his wife was having illicit relations with a neighbour. He admitted that he had no proof of this unfaithfulness but said that if he had had proof he would have run his rival through with a four-pronged gardening fork.

Progress.—The motor symptoms rapidly became worse. The left upper limb was in an abnormal position, with the arm held firmly against the trunk, the forearm semi-flexed on the upper arm, the wrist in hyperflexion and the hand in forced pronation so that the palm was turned outwards. The four last fingers were in flexion at the metacarpo-phalangeal joints but extended at the inter-phalangeal joints. The thumb was bent dorsally at a right angle as the result of a fall in 1943. The involuntary movements were of an irregular athetotic character and were maximal distally and in to the hand. There was also wide circular hemiballistic movement of the whole arm. When the latter form of movement had a specially wide range, movement of a similar character but less amplitude often appeared in the right arm.

Voluntary power was normal in the right upper limb, but on the left side he could not move his fingers voluntarily. When he walked, which he did with great difficulty, his feet were placed progressively more widely apart. The grimacing movements, which were always symmetrical, became more and more accentuated. The co-ordination of his movements in performing any but the simplest acts was poor, for example, when he tried to kiss his wife, he placed his mouth correctly against her cheek, but made the kiss too early to too late.

In January, 1944, he complained of painful cramp in his left calf, but this disappeared after a few intravenous injections of calcium.

By February, he was no longer able to stand alone, his left leg was held con-

stantly extended, with the sole turned inwards and the toes flexed. The abdominal reflexes persisted, although weak. The muscular hypertonia which had now involved the left lower limb now appeared in the right lower limb, but was always most intense in the left arm.

On April 22, 1944, the patient's condition, which had been becoming rapidly worse during the previous weeks, became suddenly grave (but without any stroke being observed). He became semi-comatose, could no longer feed himself, and had to be fed. Three days later he died without rise of temperature or any further complication.

Résumé.—A man of 44 years developed cataract in one eye and, shortly after, showed nervous symptoms consisting in wide contorting movements of the left arm and symmetrical grimacing movements. There was muscular hypotonia in all the limbs, except the left arm which was hypertonic and showed involuntary movements; an abnormal gait with a wide base and an atypical dysarthria. The hypertonus spread eventually to the left leg and finally to the right leg, which did not, however, even at the end of his life, lose its power of movement. Constant choreo-athetotic movements and wide circular movements of the left arm were superposed on a basis of contracture, and at times these movements passed over to affect the right arm but were always slighter in it. Towards the end of his life he could not stand or walk without support. On the mental side, paranoid ideas were present from the beginning of his illness and to these were added a gradually deepening dementia with loss of sphincter control.

The wide range and the combination of torsion and circumduction in the movements of the left arm recall Jakob's (1923) hemiballisms, although later writers have collected under this name very different forms of hyperkinesia. Whether it is considered that the movements of hemiballismus differ in quality from those of ordinary chorea or that the difference is only one of magnitude, it may be granted that the proximal localization of the primary movements in the limb, with later spread to all its segments, distinguish them from those of chorea minor and ordinary athetosis. No doubt similar movements may be seen in chronic progressive chorea and in certain cases of bilateral athetosis. In the present case, the choreo-athetotic movements remained limited to the left upper limb.

The contracture of the limbs on the left side, which tended to extend to the right lower limb in walking, resembled that of infantile hemiplegia. It recalled, at least in the upper limb, the illustration of Baumann's case which will be referred to later. This hypertonia developed on a basis of the generalized hypotonia, which we noticed at the beginning. The clinical picture also included an abnormal posture, at first limited to the left arm, but spreading later to the left leg.

In evolution as in symptomatology, the wide hemiballistic movements, mostly limited to the left side but tending to spread to the other arm, predominated. As the disease in this case was slowly progressive one may use either the name *hemiballismus* (Baumann, 1938) or *heredo-degenerative paraballismus* (Benedek, Rakonitz) according to whether emphasis is to be laid on the continued unilaterality of the chief motor symptoms or to the bilateral spread of some of them. Baumann (1938) described attacks of hemiballismus which were very violent and strictly unilateral, with movements at a rate of one a second. These attacks varied in frequency and were grafted on to a spinal spastic paralysis with *pes equinovarus*. No abnormal facial movements were present. The symptoms appeared at the age of 7 years, and were not known to be sequels of any febrile disease.

In the case described by Rakonitz (1933) the movements occurred symmetrically on the two sides of the body. They were aggravated by emotion and absent during sleep. They occurred frequently, were rapid, of wide range and stereotyped, with a rotating character. There was no intention tremor. The tone of all the limbs varied simultaneously. Two brothers and two of the grandparents showed identical symptoms.

The mental state of our patient presented no special features. There was no congenital imbecility, such as was present in Baumann's case. Nor were there any of the mental disturbances characteristic of chronic progressive chorea, as there were in the patient of Meszaros (1941).

Meszaros' patient was a woman of 53 years, whose illness began with brusque involuntary movements of the upper limbs, producing much clumsiness of the hands. Mentally she showed great loss of memory, confabulation, disorientation in time and space, a marked lack of attention, and loss of interest in her surroundings. As neurological symptoms, the author mentions as present at the first examination, incessant movements of the hand, of the feet and of the muscles of the face and larynx, increased by emotion and specially evident in association with voluntary movements; generalized hypotonia, inability to walk, or to stand erect; confused scanning speech. Later torsion movements of the neck, trunk and lower limbs set in, with tonic contraction fixing the musculature for a short time in an abnormal attitude now and again. Histopathological examination showed a slight rarefaction of neurons in the third and deep layers of the cortex with sclerotic and shadow cells, and glial hyperplasia especially in the 6th layer. In the corpus striatum there was cellular rarefaction with gliosis and a diffuse loss of small cells contrasting with preservation of the large neurons. In the corpus luysii there was loss of neurons with atrophic appearance of those that remained.

The case of Rakonitz is, therefore, the one which resembles ours most closely. The case of Meszaros is in fact a chronic chorea with the special feature that the movements were more ballistic than in the ordinary form of the disease. Baumann's case was one of spastic paraplegia predominantly unilateral, and associated with ballistic attacks of variable frequency.

Anatomo-pathological Examination.

The brain of Fal . . . weighed 1,120 grammes (normal weight at this age about 1,350 grammes).

Examination of the upper surface of the brain showed no abnormality. The left cerebellar hemisphere was somewhat atrophied. In coronal sections, the basal ganglia appeared rather more compressed on the right side than on the left. The centrum ovale was also rather reduced in size on the right side. The appearance of the corpus striatum did not resemble that of chronic progressive chorea. The globus pallidus was small on both sides. The right corpus luysii was specially thin, and the left was narrower than normal, but both had a normal colour. The dentate nuclei and the white matter of the cerebellum appeared reduced in size. The brain-stem showed no obvious abnormality.

Histological examination was made of frozen sections by the technique of Nissl, Spielmeyer, Scharlach R, von Braunmühl and hæmatoxylin eosin; some pieces were embedded in paraffin and stained by van Gieson's method and finally some large blocks were embedded in celloidin and stained by cresyl violet and Weil's method.

Spinal cord (fig. 2).—Only the first and second cervical segments could be examined. They showed peri-ependymal and marginal gliosis of a diffuse character and marked gliosis and demyelination of the columns of Goll on both sides. By cell stains there was proliferation of astrocytes in the same areas. No lipoid degeneration products were seen. At the level of transition between spinal cord and medulla, similar lesions were found in the nucleus gracilis but the gliosis was less dense and equally isomorphic.

Medulla.—Cellular rarefaction was seen in the dorsal lamina of the inferior olive (fig. 3) and a slighter degree at the junction of this with the ventral lamina. The latter was little changed, especially on the right.

The para-olivary bodies were intact. There was a slight myelin rarefaction in the hilum of the olives. The arcuate fibres were well stained. There was dense gliosis of the olivary laminæ and of an area corresponding to the nuclei cuneati which were rarefied and showed a dense fibro-cellular gliosis, especially on one side (fig. 4).

Pons.—The only lesions observed were in the upper levels where a symmetrical atrophy of the superior cerebellar peduncles was associated with gliosis. Early pigmentary degeneration and moderate gliosis were seen in the nucleus of the mesencephalic root of the trigeminal nerve on both sides. Early gliosis and cell loss were seen in some of the ventral and dorsal pontine nuclei.

Midbrain.—The pes was intact. There was a definite rarefaction at the decussation of the superior cerebellar peduncles with dense gliosis. Peri-ependymal gliosis was present, as well as gliosis of both nuclei rubri, especially on the right side where the lesion of the corpus luysii was greatest (figs. *5a* and 6).

The substantia nigra was studied by cell stains in serial sections, part by freezing methods and part by celloidin embedding, from the corpus luysii down to the ponto-mesencephalic junction. We adopt the terminology of Hassler. One section at the ponto-mesencephalic junction in the most caudal part of the substantia nigra

showed rarefaction especially in the groups, Spvi, Spvm and Spvl. A frozen section through the caudal level of the substantia nigra showed on the left side (fig. 6*a*) the following changes: a certain number of cells could be recognized in the zones rl, rkv, W, vRS and zRS. In the groups Spvm, Spvi and Spvz, some of the cells were preserved, and the gliosis was here less dense than normal. The groups Spcz, Spzz and Sped had disappeared completely. In the groups Spdi and Spdd, an appreciable number of cells were preserved, and the gliosis was here less dense. On the right side the section passed rather farther (rostrally) (fig. 6*b*). Here also some elements of rl, rks, vRs could be recognized. By contrast Sprm, Spvi, Spvl and Sper were uniformly rarefied. Of the group Spez scarcely anything remained and in Sped definite cellular changes and dense gliosis were very evident. Spdi could not be recognized. The celloidin section passed rather more anteriorly and was not strictly in the sagittal plane. It showed, however, in general similar lesions. The groups, Sped and Spdi, showed early changes (fig. 6*c*). The most marked rarefaction was seen in the groups Spvi, Spvl and Spev, where also the gliosis was most dense.

A section through the proximal end of the *substantia nigra*, passing through the region of the *corpus luysii*, showed relative preservation of the groups Saim, Sai and Sail. The pigmented cells of RS and those of rab1 and rab2, could also be recognized. There were also lesions in the pigmented nerve cells of the cupuliform peri-retrorubol formation with neuroglial reaction. In brief, the most affected cells groups were always those on the right side, and to a less degree the groups, Spvi, Spev, Spzv, Sper and Sped on the left side. The reticular zones were less affected.

Cerebellum.—In large sections stained for myelin (fig. 7) slight diffuse pallor of the white centres of the convolutions was seen especially on the left side (crossed atrophy). The capsule of the dentate nucleus was intact, as well as the white matter of the laminæ in the region of the vermis, the flocculi and the ventral regions. In the cerebellar cortex the loss of neurons was very slight, and uniformly spread in the cortex and the vermis. These were minimal by comparison with the lesions in the *nucleus dentatus*. There was marked rarefaction in the hilum of the nucleus dentatus on both sides and shrinkage of the lamellæ of the nucleus especially in its ventro-median part.

Celloidin sections stained by Nissl's method showed a severe cell loss in the dorsal lamellæ, the angle and the ventral lamina except in the last and most median convolution of the nucleus, where a certain number of neurons are preserved. The nucleus emboliformis was less affected. In Holzer preparation the glosis corresponded to the demyelinated areas and was proportional to it in degree (fig. 7*b*). Under higher magnifications the astrocytes here were large and numerous. The neuroglial overgrowth appeared to be contemporary in the lamellæ and in the hilum. No fatty degeneration products were seen.

Basal ganglia.—There was severe and total atrophy of the corpus luysii which was reduced to a linear band in which very few cells were preserved. The rarefaction affected the middle and internal thirds and especially the central part of the segment. On the opposite side rarefaction of moderate severity is seen in the two poles of the nucleus, especially the median pole. The part of the locus niger, which was seen in this section, has been already described. On the side on which the corpus luysii is most severely affected, pigmentary degeneration with gliosis was present.

The globus pallidus, as seen in the same section, also showed diffuse rarefaction, most severe on the side on which there was greatest atrophy of the corpus luysii. The corpus luysii appeared primarily affected in the myelinated fibres within it

and in its capsule. The latter normally stains darkly, but on the right side has completely atrophied (fig 8*a*). The *fasciculus lenticularis*, which forms its dorso-lateral part, is scarcely evident. The strio-luysial fibres (derived largely from the globus pallidus) which cover its lateral pole were also atrophied. The pallor of the efferent tract and of the commissural fibres was still more evident. The lesion on the left side was identical (fig. 8*c*) but here was only commencing. Holzer preparations of the same regions demonstrated the size of the efferent tract, the short fibres of which occupy about three-quarters of the infero-external margin of the nucleus. They also demonstrated the size of the commissural system which was larger than was expected (fig. 8*c*).

The globus pallidus was studied in discontinuous serial sections. Myelin-stained sections of the rostral region showed pallor of the external segment (fig. 9*a*). Those passing through the nucleus at its widest part and through the caudal part of the anterior commissure showed disappearance of the internal (lpi) and external (lpe) lamellæ of the pallidum; severe rarefaction of myelin in the internal (gi) and middle segments, and rather less rarefaction in the outer segment (ge). The ansa lenticularis is still visible though thinner than normal (fig. 9*b*). Other sections passed through the *corpus luysii*. These showed pallor of the internal segment, less pallor of the middle and external segments, disappearance of the internal pallidal lamina, and thinning of the external lamina. Here also the ansa was only thinned. The pes and the bundle of Vicq d'Azyr appeared normal except for degeneration of the pallido-luysial fibres in the pes (fig. 9*c*). Sections passing through the same areas and stained for cells showed severe affection of the internal and external segments of the pallidum and of the internal lamina and moderate pallor of the sub-lenticular part of the *substantia innominata* (especially of its median nuclei). More dorsally the cell loss is greatest in the external segment, less severe in the middle, and slight in the internal segment, but there is definite gliosis in the two latter segments. In the most caudal section which passes through the corpus geniculatum externum, the lesions in gi are slight, with only rarefaction in the dorsal part of the nucleus.

The area of the *faisceau pallidal de la pointe* (*tractus pallido-peduncularis*) is covered by dense gliosis. This is very definite although the rarefaction of cells is slight, as is also shown by Holzer's method. There is slight pallor of the intrinsic fibres of the locus niger especially on the right, and less definitely on the left side. By Holzer's method, old-standing isomorphous gliosis is seen here. The nucleus ruber is paler than normal and its capsule rarefied in the medio-ventral sector. Gliosis with numerous large astrocytes is seen throughout it.

Putamen.—The large cells of the putamen are rather less numerous than normal, and cellular and fibrillary gliosis is rather more dense than in a normal neostriatum. In the most caudal section, the large cells of the putamen are not, however, diminished in number and there is a normal degree of gliosis.

The thalamus.—The claustrum and the tuberal structures are intact.

Centrum ovale.—In the white matter of many convolutions as also in the frontal lobe and temporal and occipital poles, the white matter has a somewhat matted appearance. This corresponds in Holzer preparations to an early gliosis with large fibre-forming astrocytes; the presence of numerous isogenic groups indicating an active hyperplasia. No fatty degeneration products were seen.

The corpus callosum shows a slight increase in cellular and fibrillary gliosis.

In the *cortex*, there are unsystematized lesions. Chronic leptomeningitis of moderate intensity is present with numerous melanophores. The molecular zone in such areas shows hyperplasia of astrocytes and microglia. The second and third layers show in places patchy outfall of neurons, and some of the remaining cells appear sclerosed, or have corkscrew apical dendrites. In the 5th and 6th layers,

the gliosis is more dense than is accounted for by the affection of the white matter. No other noteworthy abnormality was seen.

The choroid plexuses showed no lesions.

The optic nerves and chiasma were paler than normal, especially the left optic nerve, in sections stained for myelin, with dense fibrillary gliosis especially along the septa. Cell stains show numerous astrocytic nuclei but no inflammatory lesions.

Résumé.—The lesions seen were:

(1) Marked atrophy of the pallido-luysian system.

(2) Almost as severe atrophy of the dentato-rubral system.

(3) A gliosis of the white matter of the cerebellum and cerebrum with no focal predilection.

(4) Early and moderate atrophy with gliosis of the locus niger, the pigmented nuclei of the brain-stem (from the mesenphalic trigeminal nucleus to the peri-retrorubral cupuliform nucleus and the locus caeruleus) and of the substantia innominata of Reichert.

(5) Systematized degeneration of the columns of Goll, the nucleus of Burdach, the inferior olive (the last out of proportion to any cortical cerebellar lesions) and of some pontine nuclei.

(6) Cortical lesions of common type, consisting of pallor of the second and third layers with evidence of cellular sclerosis (but without sessile plaques or argentaffine inclusions). The lesions in the basal ganglia are greatest on the right side, those in the cerebellum on the left side.

Discussion.

What is the anatomical classification of this case? It is not one of cerebellar atrophy. If we wished to place it in this group, to which in some respects it belongs, we should emphasize the marked olivary atrophy, the slighter involvement of the nuclei pontis and the special incidence on the white matter of the cerebellum, all points which bring it near to olivo-ponto-cerebellar atrophy, as also does the involvement of the locus niger. But these lesions quantitatively take second place compared with the severe degeneration of the dentate nucleus, and, even more prominent than this, the atrophy of the corpus luysii, which is striking and extreme. The latter is associated with a very marked atrophy of the globus pallidus in its rostral and middle parts. The extent of these lesions, in spite of their very systematized character, only allows of a very guarded opinion on the anatomo-pathological classification.

Clinically, again the hypotonia and the disorders of articulation and gait (widening of the base in walking) which were noticed from the first, might be attributed to disturbance of cerebellar function arising from lesions in olivary and dental nuclei, but it could with equal reason be

urged that the speech disturbance should be correlated with the involuntary movements of the face and mouth.

The choreo-athetotic and especially the ballistic movements may be correlated with the lesions of the pallido-luysial system, on the strength of what we know of the clinical signs of vascular lesions of the corpus luysii, of which there are many verified examples. Since there have been many cases of dentato-rubzal atrophy in which these movements were completely absent (Louis-Bar and van Bogaert, 1946) we consider that the affection of this system plays no part in the causation. It does not follow, however, that this degeneration is without any effect. In fact, it seems unlikely that the nucleus ruber, when cut off from the dentate nucleus and so from a large part of the cerebellar cortex, would react to atrophy of the pallido-luysial system, as it would if it had preserved its normal connections. But it remains true that degeneration of the dentate nucleus by itself does not lead to the release of involuntary movements. The corpus luysii was the most severely and widely affected of all components in the pallido-luysian complex in our case, and its degeneration was certainly not secondary. It is possible if not probable that pallidal atrophy aggravated primary atrophy of the corpora luysii, but the atrophy of the latter nuclei far exceeded in extent and severity that of the pallidal system. It is at present impossible to determine whether the lesion of the corpus luysii was the sole basis of the hyperkinetic state. There are, in fact, as shown by a case described by one of us (De Vos and van Bogaert, 1934) cases of pure atrophy of the globus pallidus (without accompanying lesion of the corpus luysii) where in association with contracture there are also grimacing and choreo-athetotic movements. On the other hand in early degeneration of the pallido-luysial system, the abnormal movements may be of smaller range and take on the character of torticollis with tremor (van Bogaert, 1941). Therefore we must adhere strictly to the following facts which emerge with certainty from our examination: *A syndrome of choreo-ballismus with hypertonus, tending to become bilateral coincided with severe degeneration of the pallido-luysial system, specially affecting the right side but also tending to become bilateral; the severity of the clinical signs on the two sides was proportional to the pallido-luysial atrophy; the associated dentate lesion was symmetrical and equal on the two sides; the lesions in the substantia nigra were slightly greater on the side of the more severe pallido-luysial lesion.*

An important fact is that the corpus striatum, the pyramidal tracts and the motor cortex were intact. We must bear this in mind in relation to what we know of chronic progressive chorea and also in relation to the hypotheses of the cortical or pyramidal origin of chorea.

Finally if in certain cases of lesion of the corpus luysii the proximity of the internal capsule suggests that a minimal lesion of the latter may be significant, such an explanation would not apply in the case of a degenerative lesion.

Is this an example of a hitherto unrecognized form of degenerative disease? We do not claim this. But it is none the less instructive to observe that heredo-degenerative paraballismus is not associated with an isolated atrophy of the corpora luysii; the degeneration in this case was complex, involving the globus pallidus also. It may be that lesions of the latter nucleus may be adequate to lead to such symptoms, and heredo-degenerative paraballismus would then be the clinical counterpart of isolated atrophy of the pallidum and not of the corpus luysii.

The case here described has a special interest from the general point of view of understanding systematized affections of the brain-stem. Pallido-luysial atrophy was combined here with an atrophy of the dentato-rubral system (the red nucleus itself remaining intact), with a partial olivo-ponto-cerebellar atrophy (in which even the component of the substantia nigra was present) and with heredo-degenerative spino-cerebellar degeneration. In its predominant clinical signs it is related both to striatal and to cerebellar disorders; in its histological lesions it crosses the frontiers of both groups. The mental symptoms, however, could not be explained by any of the systematized degenerations of the cerebral cortex.

It would be difficult to find a better example of progressive dissolution due to hereditary degeneration in different parts of the brain-stem. And from this point of view, the clinical history of the patient's sister assumes a new importance. In her also the illness began with cataract (of special type) at the age of 40, both eyes being affected within two years. This patient showed during the last years of her life attacks of delirium with crises of excitement which were chiefly nocturnal. During the last two years before her death, she developed a cerebellar ataxia, to which, during the last weeks, there was added coarse intention tremor. Thus in the sister the hereditary degeneration was predominantly cerebellar. The coarse intention tremor suggested severe involvement of the dentate nuclei which was also the site of severe lesions in the brother. The cataract in the sister appeared long before the mental symptoms, which remained slight and paroxysmal. There was never in the sister any hyperkinetic component of striato-pallidal type. Thus, in these two siblings, the abiotrophy affected in one, first and foremost the cerebello-dentate system and, in the other, first and foremost the pallido-luysial system. But the anatomical examination showed that in the latter patient the cerebello-dentate complex had also silently participated in the degeneration.

SUMMARY.

(1) Two siblings developed a mental and nervous disease, which began at about the age of 40 years with cataract, and progressed after several years to include, in the first sibling, a state of dementia, and in the second attacks of delirium with nocturnal crises of agitation; in the first sibling, progressive hemiballismus with choreo-athetosis and special forms of contracture, and in the second, cerebellar ataxia with coarse intention tremor.

(2) The anatomical examination of the brain of the first sibling showed atrophy of the pallido-luysial and of the dentate systems overlying the beginnings of olivo-ponto-cerebellar atrophy. The substantia nigra and the pigmented nuclei of the brain-stem, as well as the columns of Goll were also affected.

(3) Heredo-degenerative hemiballismus, which was present in the first sibling, does not depend on a pure and systematized degeneration of the corpus luysii. The rôle played by the pallidum may be questionable, but the anatomical examination of the first sibling as well as the clinical symptomatology of the second, indicates that these atrophies are related to the wide group of hereditary cerebellar degenerations. Heredo-degenerative hemiballismus bridges the gap between the abiotrophies of the cerebellar system and those of the extra-pyramidal optico-striate system.

LEGENDS FOR ILLUSTRATIONS.

FIG. 2.—Cervical cord (C.2). Demyelination of the columns of Goll. (Spielmeyer, frozen section.)

FIG. 3.—Medulla. Cellular rarefaction and gliosis in the dorsal lamina of the inferior olive. (Nissl, frozen section.)

FIG. 4.—Medulla. Gliosis of the laminæ of the olives, and of the intra- and extra-ciliary zones. Integrity of the system of arcuate fibres. (Holzer, frozen section.)

FIG. 5.—(*a* and *b*) Mid-brain. The decussation of Wernekink is slightly pale in the section stained for myelin (*b*) while the gliosis, as shown by Holzer's stain (*a*), is dense.

FIG. 6.—(*a* and *b*) Mid-brain. Caudal part of the substantia nigra on the right and left sides. Pallor of staining especially in the cells in the middle third of the nucleus, more pronounced on the right (*a*) than on the left (*b*). The section of the right mid-brain passes rather more anteriorly. (Nissl, frozen section.)

(*c*) Earlier cell changes in the locus niger. (Nissl.)

FIG. 7.—Cerebellum. Atrophy greater on the left side (*a*). On this side the demyelination and gliosis of the hilum of the nucleus dentatus are also more pronounced (*b* and *c*).

FIG. 8.—Extreme atrophy of the corpus luysii in the right (*a*) and on the left where it is beginning in the medial third (*b*). Corresponding gliosis on the left side (*c*).

FIG. 9.—(*a*) Section passing through the rostral part of the putamen. Pale staining of the external segment of the globus pallidum (ge).

PLATE XXVIII

FIG. 2.

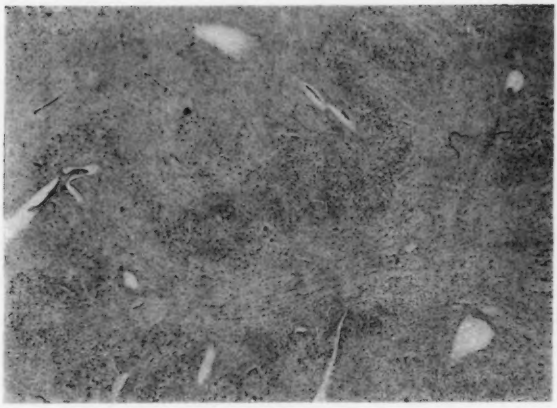

FIG. 3.

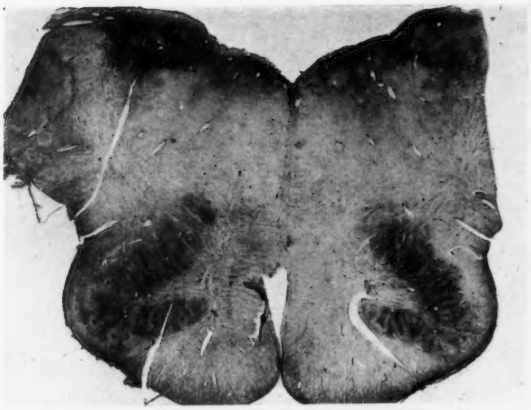

FIG. 4.

FIG. 5a.

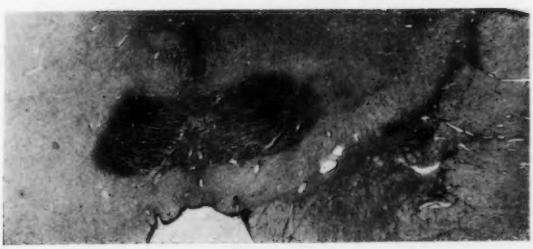

FIG. 5b.

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PLATE XXIX

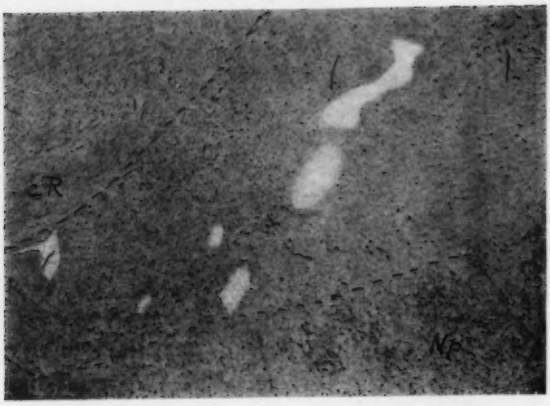

FIG. 6a.

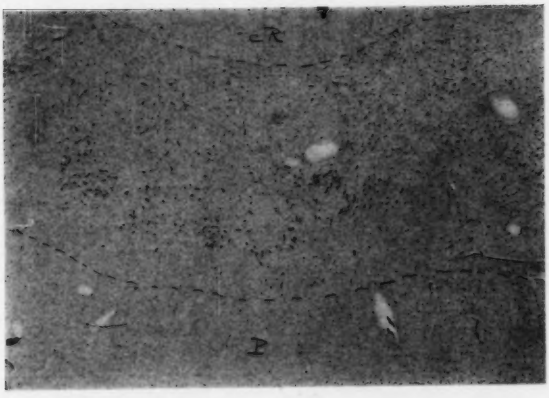

FIG. 6b.

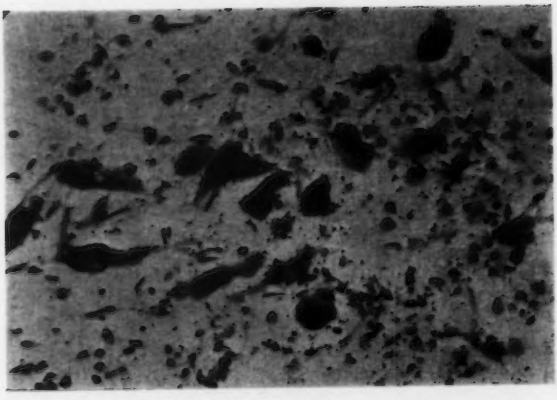

FIG. 6c

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PLATE XXX

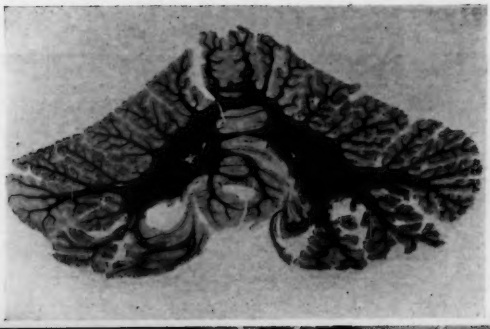

FIG. 7a.

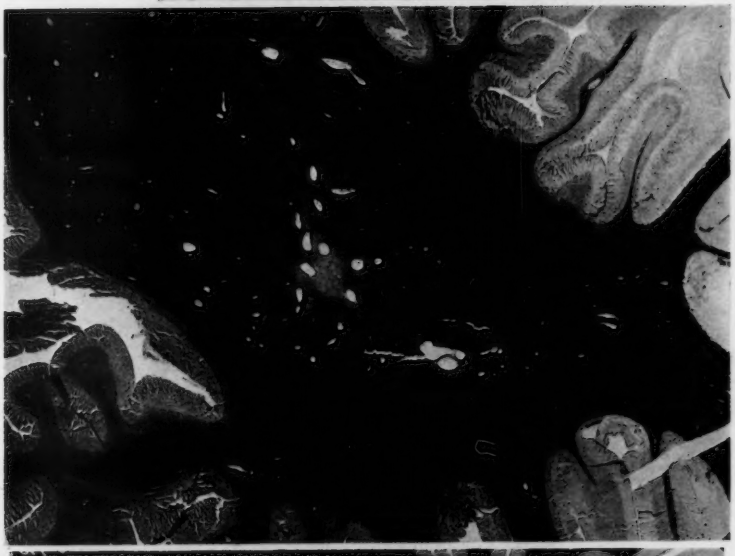

FIG. 7b.

FIG. 7c.

To illustrate article by Jean Titica and Ludo van Bogaert.

PLATE XXXI

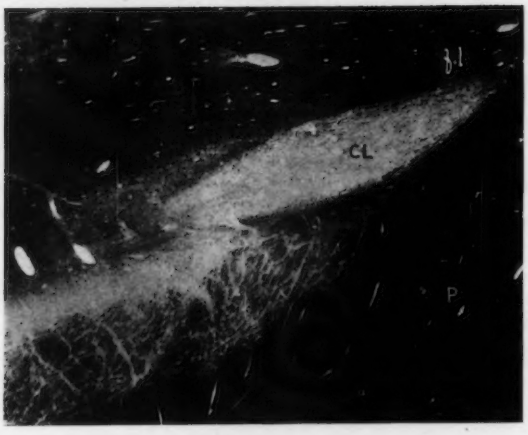

FIG. 8a.

FIG. 8b.

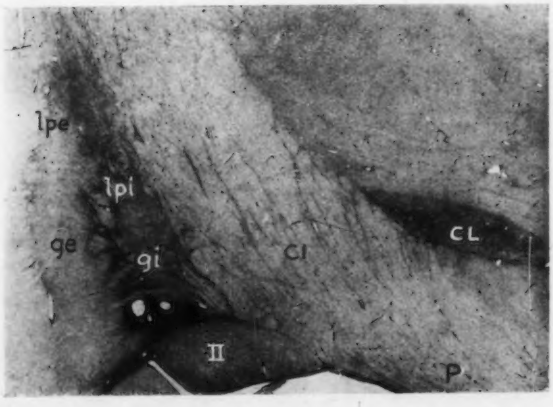

FIG. 8c.

To illustrate article by Jean Titica and Ludo van Bogaert.

PLATE XXXII

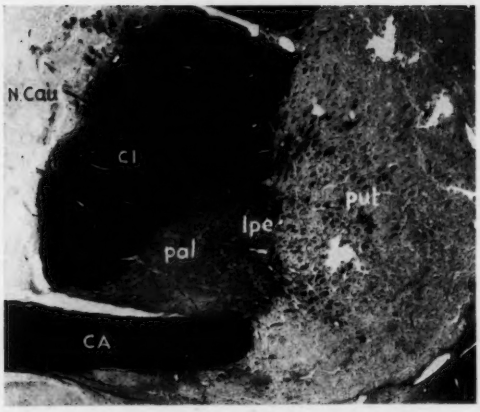

FIG. 9a.

FIG. 9b.

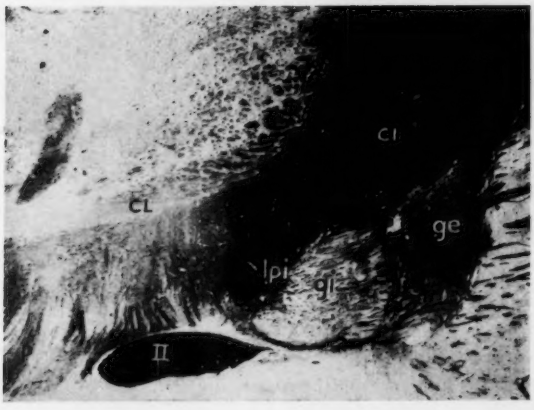

FIG. 9c.

To illustrate article by Jean Titica and Ludo van Bogaert.

PLATE XXXIII

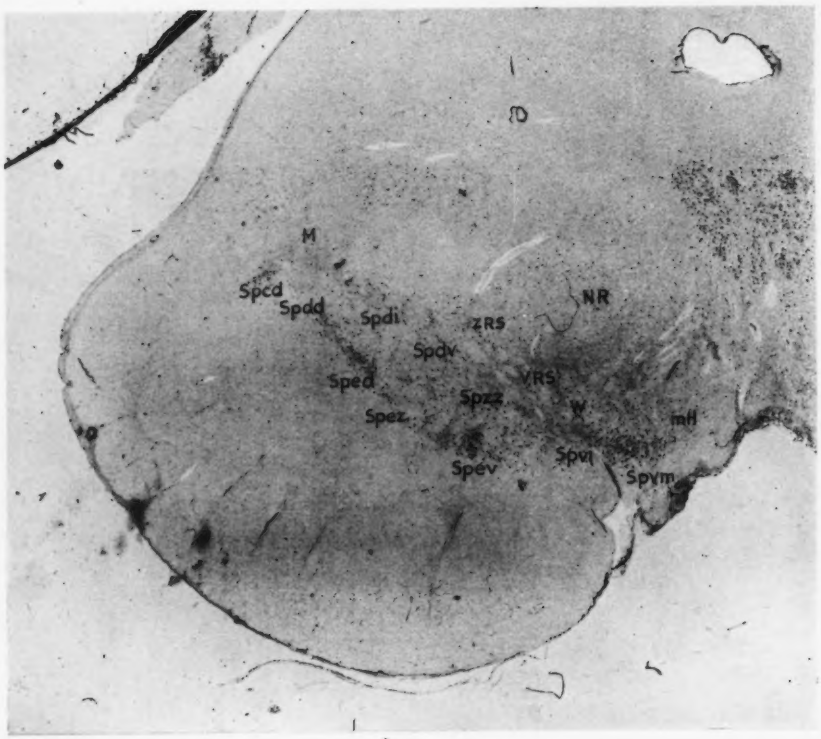

FIG. 10.

To illustrate article by Jean Titica and Ludo van Bogaert.

(*b*) Section passing through the caudal part of the anterior commissure. Disappearance of the internal and external medullary laminæ of the globus pallidus (lpi and lpe) with rarefaction of the internal (gi) and to a less extent of the external segments (ge). (Spielmeyer, frozen sections.)

(*c*) Section passing through the anterior part of the corpus luysii. Rarefaction of gi and of the ansa lenticularis. (Weil, celloidin section.)

FIG. 10.—Section of mid-brain to indicate the cell groups in the substantia nigra referred to in the text. The letters correspond to the nomenclature adopted by the Vogts (1942).

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STRIATAL AND PYRAMIDAL LESIONS IN THE CAT.

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Introduction.

In an earlier paper (Liddell and Phillips, 1940) we have reported observations on the effects of chronic circumscribed injuries of the caudate and lenticular nuclei in cats. A critical evaluation of these experiments, stressing the small amount of descending degeneration in mid-brain, medulla and cord in some cases, and complete absence of any such degeneration in others, led us to the conclusion that the contralateral extensor hypertonia resulting from these lesions was due specifically to the striopallidal damage. There was no positive evidence of unintended corticospinal involvement, whether by trespass on the internal capsule or by interruption of "aberrant" corticospinal fibres coursing in the basal grey matter. In this connection, however, Lassek's (1942*a*, *b;* Lassek and Rasmussen, 1940) recent careful descriptions of the fibre-composition of the pyramids in several species warn against implicit confidence in the application of myelin techniques to the pyramidal system, a fibre-population of which some 40 per cent. are unmyelinated, the remainder being, for the greater part, fibres of small calibre, for which myelin methods are not reliable.

The effect on posture of corticospinal interruption in the cat having been the subject of some disagreement in the literature, we studied a series of cats in which histologically-verified lesions had been placed in one or both medullary pyramids, and concluded, as Ranson (1932), Marshall (1934) and Evans and Ingram (1939) had done, that crossed extensor hypertonia is the invariable consequence of uncomplicated section of a medullary pyramid in this species (Liddell and Phillips, 1944). The possibility, therefore, remained that impaired corticospinal function, even if unrevealed by coarse structural damage, might have been responsible for the finding of extensor hypertonia in cats with lesions centred in the basal ganglia.

Decisive evidence against such an event could be obtained from preparations in which, after preliminary interruption at the medullary level, one or both pyramidal tracts had been allowed to degenerate completely.

If, in such a preparation, the released extensor posture due to the primary pyramidal injury showed an increment in consequence of the newly superimposed striatal one, corticospinal participation in this fresh release could be absolutely excluded. Such findings form the subject of the present paper.

Methods.

Tame 2·5 kg. cats, usually female, have been used in these experiments. Ten of them have been observed over periods ranging from 128 to 540 days with final anatomical control. One died of cerebral abscess and was rejected. At the first operation, the medullary pyramids have been sectioned by Starlinger's approach, using the special precautions already described (Liddell and Phillips, 1944). Bilateral preparations have been made in two stages, usually with a week's interval. 50 to 240 days later, electrolytic lesions were placed in one lenticular nucleus (the ipsilateral one in cases of unilateral pyramid section), using 0·75 mm. diameter concentric needle electrodes, enamelled except at their tips, and directed into the brain by a Souttar-Beattie stereotaxic instrument (Liddell and Phillips, 1940). For each lesion a current of 5 ma. flowed for five minutes. In 4 animals, similar lesions were made in the ipsilateral caudate nucleus 75 to 160 days later. These intervals have been sufficient, in every case, to allow a steady neurological base-line to be reached. The methods of neurological examination have been previously described in detail in the papers to which reference has been made. When the observations were complete, the brains were fixed by perfusion in situ with formaldehyde-saline. Blocks of hemisphere containing the whole basal lesions were embedded in paraffin, cut in serial 20 μ sections parallel to the vertico-transverse bregmatic-chiasmatic plane (one of the zero planes of reference of the stereotaxic apparatus), and stained by Weil's method. The whole medulla has also been cut in serial sections and similarly stained, and sections of cervical cord have also been examined. In some cases, animals have been killed after the basal injury at an interval appropriate for the detection by Busch's or Marchi's method, of any recent descending degeneration in frozen sections of cerebral peduncles and cord.

Results.

Complete division of one or both pyramids is attended by comparatively minor postural or motor defects in the spontaneous behaviour of cats. Where nembutal has been used, severe crossed paresis may not even outlast the anæsthetic if, as is usually the case, action of the drug persists for more than twelve hours. In the few cases in which ether was chosen, it was sometimes observed that for a few hours at most, the contralateral limbs collapse easily beneath the body-weight, or scissor helplessly against their normal fellows. For a few days definite weakness of flexion of the affected foreclaws is evident in such activities as grasping at a moving ball of paper in play, or when scaling the wire mesh covering the windows, when these claws do not adequately engage the wire, but slide down over it in a ratchet-like manner. On a slippery surface, the affected limbs, on taking weight, may slide passively into abducted attitudes. After a week or more the animal enters a steady

state in which no gross abnormality impresses one on superficial examination. In walking on a level floor there may be some circumduction of the crossed hind-limb, with occasional scraping of the toes. This effect is always clear-cut in both hind limbs after bilateral lesions, and remains as a permanent tendency. Real disability is only brought out in situations demanding unusual locomotor skill, such as walking along a horizontal ladder (Marshall, 1934) or pipe, but this clumsiness improves considerably, though not completely, with experience over a period of months. The contralateral extensor hypertonia and deficient placing reactions (Bard, 1933), however, are permanent.

The abnormalities resulting from unilateral injury to the striopallidum are likewise inconspicuous. This injury also determines a crossed extensor rigidity, associated with clumsiness on the horizontal pipe and with defective placing reactions, but there is no paresis at any stage of recovery. A striking feature is circling in the direction of the injured side, which is invariable in the first few days. It is evidently compulsive, for it is commonly noticed that it may carry an animal's head past a desirable goal, such as a dish of food, to which it may succeed in returning only after one or more complete revolutions. Mettler and Mettler (1942) regard the circling in cases of unilateral lesion as "simply one-half of the pattern of cursive hyperkinesia" found in cases of bilateral frontal and striatal damage.

The syndromes of pyramidal and of basal lesion are simply combined in preparations which are the seat of both. In every case, the second (lenticular) operation has increased the contralateral extensor rigidity due to the previous pyramidal section, and where a third (caudate) operation had been performed, this has increased the rigidity still further. There has never been any recrudescence of the initial paresis. Nembutal was the anæsthetic for all the stereotaxic operations, so that transient paralysis for the few hours after the lesion would not have been evident. But the characteristic circling movements have always declared themselves, even in those cases in which complete division of both pyramids had been achieved initially.

The foregoing general account is amplified by summaries of the postural changes in the individual experiments. The general features of the syndrome in each case have already been described. The anatomical basis of each experiment is summarized in camera lucida diagrams of appropriate sections from each series, each with a brief annotation. These tracings are chosen to indicate the main locus of each lesion, the annotation being based on examination of the series as a whole. Terminology

is that of Winkler and Potter's (1914) atlas. The millimetre scale on each tracing measures the fixed and stained material which owing to shrinkage is 8% to 10% smaller than in the fresh state. Anteroposterior lengths are measured by counting the 20 μ sections in the series and are thus subject to the same shrinkage error.

I.—*Unilateral pyramid section followed by ipsilateral lenticular electrolysis.* (2 cats.)

Cat 1 (August 16, 1940). Operation for section of right pyramid (fig. 1).

FIG. 1.—Cat 1. Camera lucida tracing of section through centre of the medullary lesion (solid black) at the level of the inferior olives: lateral four-fifths of right pyramid destroyed: inferior olive severely injured: ascending degeneration in right medial fillet: descending degeneration in outer two-thirds of right pyramid: heavy circumscribed degeneration in left dorsolateral region of cervical cord.

On the day after operation left hind limb was fully extended when cat was nursed in the observer's lap, the pad-reading 2·5 kg. when the rigidity was forcibly overcome by pressure from spring dynamometer: toes spread: dynamometer reading of right hind limb 1·0 kg., difference 1·5 kg. The difference subsided over a period of five months, as usual in cases complicated by olive and fillet damage.

Eight months after the first operation (April 18, 1941) two lesions were placed in the right lenticular nucleus (fig. 2).

Weight 2·9 kg.

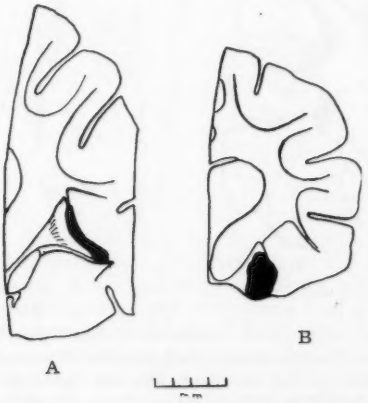

FIG. 2.—Cat 1, lenticular lesions. A, The posterolateral lesion in external capsule, claustrum and putamen. B, Section incomplete inferiorly, the anteromedial lesion in putamen, globus pallidus, anterior commissure and

amygdala. The posterolateral lesion measures 6·4 mm. anteroposteriorly, and the anteromedial 2·8 mm. Internal capsule intact. No degeneration in Busch preparations of cerebral peduncles and cervical cord. The two needle tracks, not shown, 0·3 mm.

Throughout a further 35 days' survival a conspicuous degree of left-sided extensor rigidity, which had reasserted itself immediately after the second operation, persisted without reduction. The dynamometer readings showed a difference of 1·0 to 1·5 kg. between the two hind-limbs, and the rigidity was now clearly evident in the gait.

Cat 2 (June 26, 1941). 1·9 kg. female. Right pyramid severed (fig. 3).

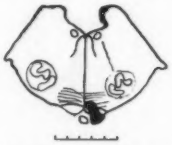

FIG. 3.—Cat 2, right-sided medullary lesion, at level of trapezoid body and superior olive. Descending degeneration of pyramid complete but for extreme lateral and medial fibres: circumscribed left-sided dorsolateral degeneration in cervical cord: olives undamaged: small amount of ascending degeneration in axial fibres of right trapezoid.

Initial difference in dynamometer readings of over 1·5 kg. between the affected and normal hind limbs: 1·0 kg. after three weeks, and so remaining for the remaining 102 days. Then (October 8, 1941) two lesions were placed in the right lenticular region (fig. 4), and the animal was kept for further 423 days.

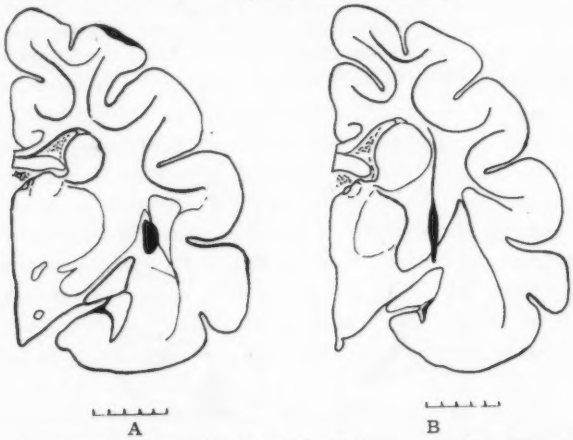

FIG. 4.—Cat 2, right-sided lenticular lesions. A, The posterolateral lesion, 2·5 mm. in length, in external capsule, claustrum and putamen. B, The anteromedial lesion, 1·0 mm. long, in centrum, internal capsule, and junction of putamen with outer segment of globus pallidus. The small capsular injury caused no detectable degeneration in the cerebral peduncle (Weil's method). In A, note the small vascular lesion, due to the track of the needle, in overlying cortex. Extensive diathermy burns of this region produce no signs (Liddell and Phillips, 1940).

At regular examinations after the second operation, the difference between hind limbs was found to have increased to 2·0 or 2·5 kg. (e.g. left hind 3·2 kg., right hind 1·2 kg.). This continued for a year and more. At the time of death the body-weight was 2·6 kg.

II.—*Unilateral pyramid section followed first by ipsilateral lenticular electrolysis, and later by ipsilateral caudate electrolysis* (2 cats).

Cat 3 (June 11, 1941). 2·1 kg., female. Left pyramid cut (fig. 5).

FIG. 5.—Cat 3, lesion of left pyramid, trapezoid level. Olives uninjured: small penetration of left trapezoid, and small ascending degeneration in its axial fibres. Descending degeneration in intermediate third of left pyramid, and in dorsolateral region of cervical cord on the right.

At first, hypertonia in right hind was marked, 3·0 kg., left hind 1·5 kg., but after fourteen days difference fell to 1·0 kg. and continued so for the rest of forty-five days. Two lesions were then placed in the left lenticular region (fig. 6) (July 26, 1941).

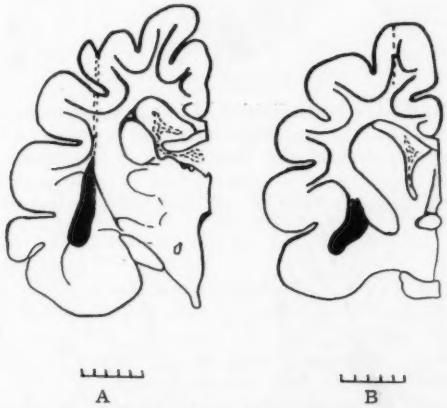

FIG. 6.—Cat 3, A, posterolateral, and B, anteromedial lenticular lesions. A is 5 mm. in anteroposterior extent, and injures the claustrum, external capsule and putamen; B, 1·8 mm. long, lies in the putamen and involves also external capsule, claustrum and outer segment of globus pallidus. No degeneration in cerebral peduncle.

The difference between the dynamometer readings for the extensors of the hind limbs at once rose to 2·0 kg., but fell slowly to 1·5 kg. during a 75-day interval. Finally (October 10, 1941) three lesions were placed in the left caudate nucleus (fig. 7), and the cat observed for a further 422 days. At first the hind-limb difference was 3·0 kg., right 4·0 kg., left 1·0 kg., a striking condition in an animal weighing only 2·3 kg. This difference declined to 1·5 kg. in about six months.

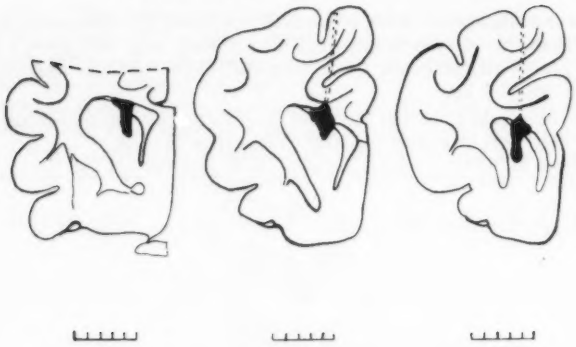

FIG. 7.—Cat 3, A, B, and C. The posterior, middle and anterior caudate lesions are fused into a single composite lesion 5·0 mm. long. Degeneration extends caudally in the subcallosal fasciculus (Mettler, 1941).

Cat 4 (March 11, 1941). 2·2 kg. female. Section of left pyramid (fig. 8).

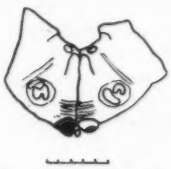

FIG. 8.—Cat 4. Complete division of left pyramid, with small lesion in right pyramid. Level of trapezoid body and superior olives. The left pyramid completely degenerated: heavy crossed dorsolateral spinal degeneration: small degeneration in ventral part of right pyramid: minimal ascending degeneration in most ventral axial fibres of trapezoid.

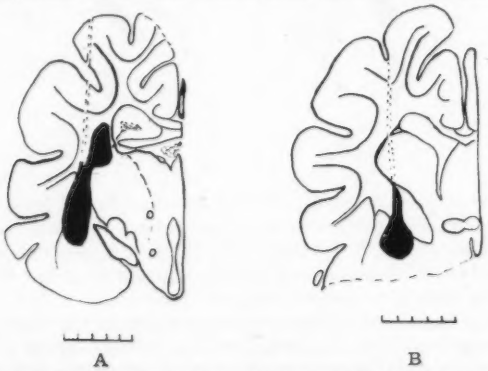

FIG. 9.—Cat 4, lenticular lesions. A, posterolateral, 3·5 mm. in length, lies in putamen, external capsule, claustrum and corona. B, antero-medial, is in putamen and outer segment of globus pallidus, encroaching on inner segment of globus pallidus and internal capsule, 2·6 mm. in length. Its

most anterior part interrupts the anterior commissure (*see* fig. 10 A). Caudally, gross degeneration of stratum sagittalium internum (Winkler and Potter, 1914) extends towards the occipital lobe. There is some diffuse degeneration in the left cerebral peduncle, most marked in its intermediate third.

The contralateral limbs were hypotonic for the first week but a few days later hypertonia was well established, a difference of 0·8 to 1·0 kg. being consistent. This transient hypotonia has been attributed to temporary œdema spreading to the medial fillet (Liddell and Phillips, 1944). Fifty days after the pyramidal operation (May 1, 1941) two lesions were placed in the left lenticular region (fig. 9 and fig. 10 A), increasing the rigidity in the right limbs by a small but definite degree to a difference of 1·0 to 1·5 kg., which persisted for 160 days, when (October 10, 1941) three lesions were placed in the left caudate (fig. 10). The right extensor rigidity then greatly increased to 4·0 kg. in the right hind limb as against 1·5 kg. on the left, a difference of 2·5 kg. (body-weight 1·9 kg.).

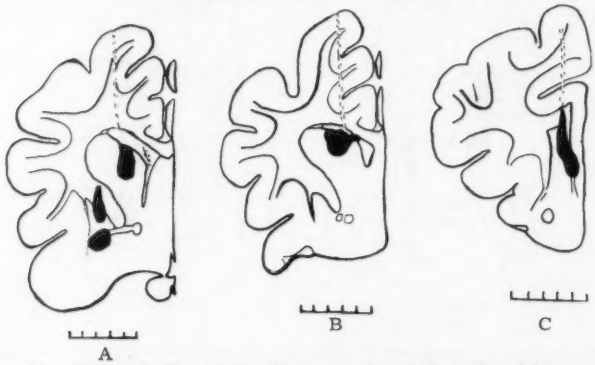

FIG. 10.—Cat 4, A, B, and C. Three caudate lesions fused into a single lesion 4·5 mm. long. In B and C the anterior needle tracks are seen in the posterior part of the cruciate sulcus. A also shows the anterior part of the lenticular lesion.

There was no decline in the rigidity in sixty days.

III.—*Bilateral pyramidal section followed by unilateral lenticular electrolysis* (4 cats).

Cat 5 (August 20, 1941). Female. 2·2 kg. Section of right pyramid. Convalescence marked by severe post-operative pneumonia, treated with sulphapyridine. This precluded detailed observation for a fortnight, when dynamometer readings were: right hind (normal) 1·0 kg.; left (affected) 1·7 kg. A month after the operation, with full recovery in health, the affected limb read 2·5 kg. as against 0·0 kg. on the normal side. The left pyramid was then cut (September 18, 1941). Both lesions are shown in fig. 11.

FIG. 11.—Cat 5, medullary lesions. Trapezoid level. The initial operation had completely severed right pyramid without penetrating the

trapezoid deeply enough to cause axial ascending degeneration. The second operation, while complete with respect to the left pyramid, had entered the trapezoid, and some ascending degeneration could be followed up the medial fillet system. Heavy symmetrical dorsolateral degeneration in cervical cord.

Both hind limbs were then hypertonic, but left persistently more, 0·4 kg. difference. This was due to the absence of fillet injury on the right side and its presence on the left, where it prevented the full development of extensor rigidity which uncomplicated left pyramid section would have brought about in the right limbs. The condition was stationary for eighty days. As the left limbs were the more affected the right lenticular nucleus was chosen for electrolysis on December 9, 1942. Two lesions were placed therein (fig. 12) and a further eighteen days' survival allowed, when the cat was killed for Marchi studies.

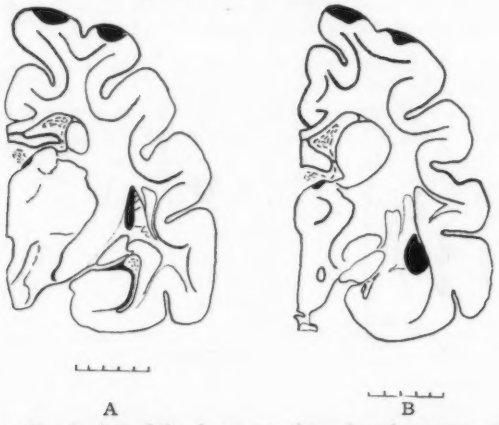

FIG. 12.—Cat 5, A and B, the posterolateral and anteromedial lesions in the right lenticular nucleus. A is 1·6 mm. in length and lies along the inner border of upper part of putamen. B is 2·1 mm. in length and occupies the lower half of the putamen 2 mm. in front of A. Marchi studies showed absence of degeneration in cerebral peduncles. The internal capsule was nowhere injured. The needle tracks, not shown, were 0·3 mm. diam. except in the cortex, where each had caused a small hæmorrhage. This region has been injured without effect in previous control experiments.

The effect was further to increase the rigidity in left limbs, the hind-limb difference rising from 0·4 to 1·4 kg. for remainder of experiment.

Cat 6 (October 27, 1941). Female, 1·6 kg. Section of left pyramid, followed by usual extensor rigidity of right limb. A week later (November 5, 1941), section of right pyramid (fig. 13).

FIG. 13.—Cat 6. Medullary lesions. Trapezoid level: both pyramids completely severed: trapezoid is penetrated on both sides and more rostral

sections show some degeneration in its axial (fillet) fibres, a little more on the right side than on the left. Caudally, both pyramids completely degenerated. There is severe circumscribed degeneration in both dorso-lateral columns of the cervical cord.

Because of mild pneumonia subsequently, no examinations were made for ten days, but for the remainder of fifty days both sides showed an almost equal amount of extensor hypertonia, both hind limbs reading 1·8 to 2·5 kg., equally on each occasion, though right side sometimes 0·1 kg. more than the left, commensurate with the slight asymmetry of the minimal fillet damage. Left lenticular region was then injured (fig. 14).

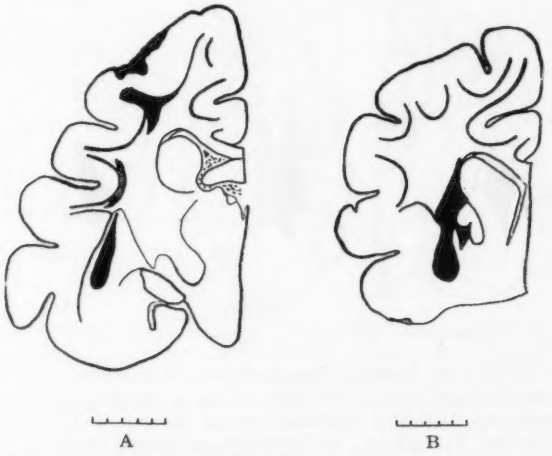

FIG. 14.—Cat 6. Lesions in the left hemisphere. A, posterolateral, 1·8 mm. long in putamen. There are also vascular injuries in the track of the needle, in particular to the cortex of gyrus suprasylvius medius and to its medullary cone. B, the anteromedial lesion in putamen and globus pallidus, 4·8 mm. in anteroposterior length. This lesion extended across the whole thickness of the internal capsule as far as the lateral aspect of the caudate. Forward from this, degeneration passed into the anterior part of the centrum semiovale. Little degeneration in cerebral peduncle.

Although complicated by hæmorrhages in track of posterior needle and by extension of anterior lesion into internal capsule, there was successful and severe lenticular injury, both pyramids having previously degenerated completely. It is, therefore, significant that the right hind limb showed an increase of 0·8 to 1·0 kg. over the readings given by the left limb, consistently throughout ninety days' survival. Characteristic values were: Right, 2·4 kg., left, 1·5 kg. Both were hypertonic. The body-weight at the end of the experiment had risen from 1·6 to 2·9 kg.

FIG. 15.—Cat 7. Lesions at trapezoid level, completely dividing both

pyramids, but penetrating trapezoid and causing clear-cut ascending fillet degeneration. Caudally, both pyramids completely degenerated. Heavy circumscribed bilateral cervical cord degeneration (dorsolateral region).

Cat 7 (June 25, 1941). Male, 2·5 kg. Left pyramid severed with ensuing right-sided hypertonia.

A week later (July 3), right pyramid severed (fig. 15): observed over 130 days. As would be expected from the terminal histological findings, the degree of extensor release in this animal was less than in the cases of pure pyramidal lesion: both read about 2·0 kg. On November 13, 1941, three lesions were placed in the left lenticular region (fig. 16).

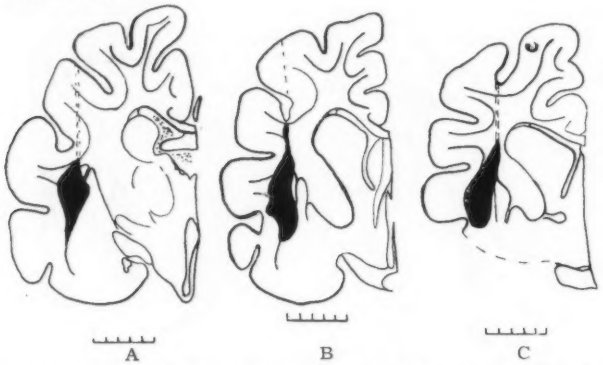

FIG. 16.—Cat 7. Posterior, intermediate and anterior lesions are fused into a single composite lesion 6·6 mm. in length, injuring the whole length of putamen and claustrum. No degeneration in cerebral peduncle. Needle tracks 0·3 mm. in diameter; no hæmorrhages related to them.

An increase of 1·0 kg. at once declared itself in the right hind limb, and this difference between the two sides persisted for the remaining thirty days of observation.

Cat 8 (January 29, 1941). Female, 1·4 kg. Both pyramids cut at one operation (fig. 17).

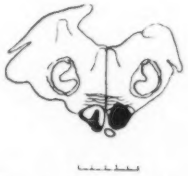

FIG. 17.—Cat 8. Medullary lesions. Division of pyramid complete on right; intermediate third destroyed on left: trapezoid penetrated on right, causing some ascending fillet degeneration. Caudally, right pyramid completely degenerated, and a ventrally-placed wedge of intermediate third of left pyramid also degenerated. Cervical cord: heavy dorsolateral degeneration on left, less well marked on right.

Over 190 days no well-marked hypertonia, and but little inequality, readings of 2·0 kg. right and 2·2 kg. left being not unusual. Retrospectively, this can be

related to the anatomical findings: an incomplete pyramidal injury on left, without fillet involvement, causes a postural abnormality in right limbs comparable to that produced in left limbs by a complete right pyramid section whose effect is reduced by fillet damage. In view of the slightly increased extensor posture on left, right-sided lenticular lesions were made (April 24, 1941) (fig. 18). During the last 35 days' observation the left hind limb gave readings consistently 1·0 to 1·5 kg. in excess of the corresponding ones on the right. It should be remembered that the right pyramid was previously the seat of complete lesion.

FIG. 18.—Cat 8. Two lenticular lesions, the anteromedial 6 mm. in length, the posterolateral 2·2 mm. The former lies in the internal capsule and globus pallidus, the latter in the putamen and outer segment of the globus pallidus, transgressing also the internal capsule. Sections of cerebral peduncle and cervical cord stained by Busch's method show no fresh degeneration. (35 days' survival.)

IV.—*A control: unilateral pyramidal section, followed by massive electrolytic injury to internal capsule without injury to the striatum: later caudate electrolysis.*

Cat 9 (April 23, 1941). Female, 2·1 kg. Left pyramid cut (fig. 19); release of right extensor hypertonia followed and was stationary for 85 days. (Right hind 2·0 kg., left 1·0 kg.)

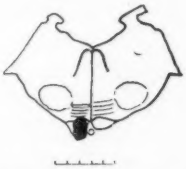

FIG. 19.—Cat 9. Lesion at trapezoid level. Division of left pyramid is all but complete; only the most medial and most lateral fibres survive at lower levels of the pyramid, and there is gross circumscribed degeneration in the right dorsolateral column of the cervical cord. No ascending degeneration.

Then (July 19, 1941) two electrolytic lesions, aimed at the left lenticular nucleus, fell wholly within the internal capsule, and without injuring the lenticular or caudate nuclei (fig. 20).

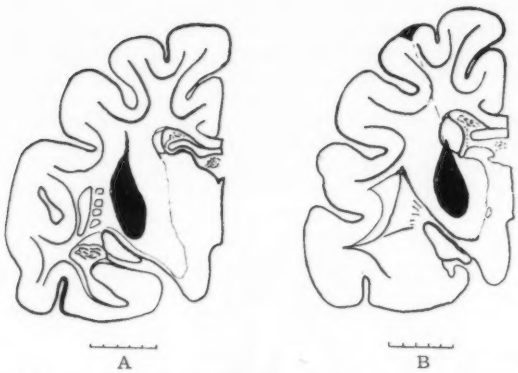

FIG. 20.—The lesions in the internal capsule in cat 9. A, the posterior, is 2·24 mm. in length; B, the anterior, is 2·56 mm. in length. No injury to striatal grey matter. Heavy degeneration in the intermediate one-third of the cerebral peduncle.

This in no way affected the existing extensor rigidity, either immediately or at any time during the next 85 days. On October 15, 1941, three lesions were successfully placed in the left caudate (fig. 21). These lesions were small and discrete, in contrast to the larger and fused lesions in the caudates of cats 3 and 4, and they produced a smaller, though quite definite, increment in the rigidity of the right limbs. The final dynamometer readings were 2·0 kg. on the right and 0·6 kg. on the left. The animal was killed 50 days after the third operation.

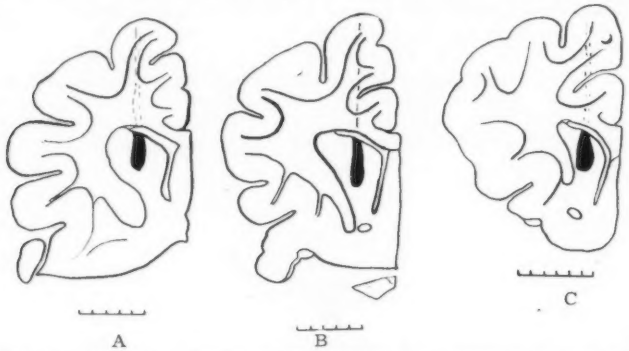

FIG 21.—A, B, C. Posterior, intermediate and anterior lesions in the left caudate of cat 9. A, 1·2 mm. in length, B, 0·9 mm., C, 0·8 mm. These lesions are well separated—there is no fusion.

DISCUSSION.

In 1941 Professor S. W. Ranson (personal communication), commenting on our previous experiments (Liddell and Phillips, 1940), suggested that the results might have been due to corticospinal injury. Arguing

that pyramidal and striatal lesions in his experience both caused extensor rigidity in cats, whereas monkeys both failed to do so, he deemed it more likely that the common factor in each case was the corticospinal injury, than that the same relatively constant syndrome should result from damage to such different structures as the putamen, claustrum, globus pallidus and subthalamic region. The experiments now reported were at that time in progress, but were insufficiently advanced to justify a definite answer. These experiments are technically difficult in the cat because the basal ganglia, more particularly the globus pallidus, are not only smaller but also less compact than those of higher forms, but we believe that our small series is significant in view of the consistent finding of an increase in the residual pyramidal rigidity following striatal lesion, coupled with detailed anatomical control. Striatal lesion was the common factor in every case. In cats 1, 3 and 5, there was no involvement of adjacent white matter, except for the fine needle tracks. Cortical or subcortical hæmorrhages were found in the path of the needle near the junction of the sulcus lateralis with the sulcus ansatus in cats 2, 5, 6 and 8; but we have previously shown (1940) that control diathermy burns 5 to 10 mm. in diameter in the cortex of this region are without effect on posture. The ipsilateral pyramid had been completely interrupted in cats 4, 5, 6, 7 and 8 and all but completely in cats 1 and 2. In cat 9, a lesion confined to the internal capsule, leaving untouched the basal grey matter, caused no increment in the residual rigidity due to previous complete pyramidal section on the same side. In contrast, a later caudate injury, smaller than usual, did result in a small but definite increase.

This evidence, therefore, so far as the cat is concerned, establishes, we believe, that the crossed hypertonia following striatal lesion is the specific result of that lesion and is not due to damage to the pyramidal tract as classically defined (fibres composing the medullary pyramid: *see* Marshall, 1936).

It has to be admitted that the anatomical basis of the pyramidal system is less firm at the present time than it was ten years ago. The conception of the pyramidal tracts as arising from specific cells in a sharply limited cortical area and comprising the entire bulk of the medullary pyramids has been seriously questioned for several species (Levin and Bradford, 1938; Lassek, 1941, 1942*c*, 1943; Lassek and Wheatley, 1945; Walshe, 1942). There is agreement, however, that most (Lassek and Evans, 1946), if not all (Brouwer, 1920 (cat 1); Bard and Rioch, 1937; Glees, to be published; Mettler, 1945) of the axial fibres in the pyramids do degenerate in several species following complete decortication. If this

is so, it still seems justifiable to suppose that a complete lesion of a medullary pyramid will interrupt most, if not all, of the fibres forming the direct corticospinal pathway.

The possibility remains that collaterals of corticospinal axones (which survive rostral to the level of section—Lassek, 1942*d*), or corticopontine, corticonigral or other descending projection systems might have been injured in our experiments. In cats 4, 3 and 5, however, there was no injury to cerebral white matter. In cats 1, 5 and 8, Marchi or Busch examinations revealed no descending degeneration in the mid-brain, and none was found in the Weil preparations in cats 2, 3 and 7; but as Lassek (loc. cit.) and others have emphasized, fine myelinated as well as unmyelinated fibres cannot be traced by these methods, and too much stress cannot, therefore, be laid on such negative findings.

Combined red nucleus and pyramidal lesions in the hands of Evans and Ingram (1939) have given results similar in many respects to our own. We agree with them that the summed rigidity from these lesions is less intense than decerebrate rigidity. Decorticate rigidity also is less than decerebrate (Bard *et al.*, 1924; Liddell, 1937), although more intense than that following complete pyramid section (Liddell and Phillips, 1944). Marshall (1935) found that the rigidity of pyramidal section was increased by injury to the motor area in the cat.

From an analysis of their results of frontal lobe injury in 50 animals, Mettler and Mettler (1942) have concluded that the resulting hypertonia is more intense if the caudate is involved than if the frontal cortex alone is destroyed.

The relatively minor disorders of posture and of locomotion following these combined injuries are less surprising when it is remembered that these functions in the cat are seemingly little disturbed by complete decortication (Dusser de Barenne, 1920; Schaltenbrand and Cobb, 1930; Bard, 1933; Bard and Rioch, 1937; Liddell, 1937). Ablation experiments, such as those of Evans and Ingram (1939) and our own, in an animal in which, as in the cat, the effects of injury to different parts of the motor system are quickly compensated, are of limited scope. If, as in the present observations, postural mechanisms are permanently released, it may be concluded that under normal conditions the activity of the parts destroyed—in this case the caudate and lenticular nuclei—exercises a tonic inhibitory influence over the activity of other levels. Such a conclusion is impressively demonstrated by stimulation (Mettler *et al.*, 1939) and recording (Dusser de Barenne and McCulloch, 1938) techniques.

SUMMARY.

It is concluded that the further release of limb posture by striatal lesion in cats without pyramidal tracts is the specific consequence of impairment of striatal activity as it cannot be due to incidental injury to the cortico-spinal system.

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TRAUMATIC AMNESIA

BY W. RITCHIE RUSSELL AND P. W. NATHAN.

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INTRODUCTION

THE disturbances of memory associated with head injury are varied and worthy of special study. The most obvious clinical abnormality which accompanies many head injuries is an instantaneous paralysis of brain function—motor, sensory, reflex and mental. The term *concussion* is often used to describe this phenomenon. It is obvious that during the period of brain paralysis there can be no registration of surrounding incidents and accordingly there is subsequently a permanent amnesia for events occurring during this time. As consciousness returns the mental functions recover as after an anæsthetic, the more complex being the last to return to their normal state. While in slight injuries the stages of recovery occupy only a few minutes, after severe trauma recovery of brain function may occur very gradually during a period of several days or weeks. The stages of recovery, however, are often similar whether they run a brief or prolonged course. The function of memory is usually regained at about the same time as the last trace of confusion disappears, and the period of post-

traumatic amnesia (P.T.A.) is then at an end. The duration of the P.T.A. can be roughly ascertained, as Russell (1932) has pointed out, by asking the patient at any time *after* he has finally emerged from the state of confusion, when he "came to himself". This end-point, however, is sometimes ambiguous, for, as Symonds has emphasized, the patient's first memory after the injury, though clearly described, may be followed by a further period of amnesia for hours or days. In such cases the patient is usually able to record the time or date from which he has continuous memory, and this has been used by us for the measurement of the P.T.A. in the cases to be described. It is thus only in the later stages of mental recovery that the patient becomes sufficiently aware of his surroundings to commit them to memory and thus to end the period of post-traumatic amnesia.

Post-traumatic Amnesia (P.T.A.)

The duration of post-traumatic amnesia (P.T.A.) can only be estimated with accuracy after the patient has recovered from even slight degrees of confusion. This duration of P.T.A. will then usually remain relatively constant and will form a permanent index of the duration, not of unconsciousness, but of impaired consciousness. The P.T.A. therefore provides a useful clinical guide for the physician who may enquire into the case for the first time long after the injury occurred. It is obvious that the duration of P.T.A. will provide some indication of the severity of the general brain commotion caused by the injury, and studies by Symonds and Russell (1943) indicated its usefulness in prognosis. We have again analysed these Service cases with reference to subsequent fitness for *full duty* in a series followed up successfully through the Unit medical officers. The results are given in Table I and indicate clearly that the prospects of good recovery of efficiency diminish rapidly as the P.T.A. lengthens.

Table I.—Follow-up.

Duration of Post-Traumatic Amnesia compared with future fitness for *full duty* —based on follow-up of surviving cases six to twenty-four months after discharge from hospital. Cases were those admitted in the acute stage and therefore relatively unselected. Only those followed-up successfully are considered.

Duration of P.T.A.	*Total cases admitted to hospital*	*Ret. to duty from hospital*	*"Fully duty efficiently" on follow-up*	*Per cent. of total*
Nil	29	28	25	86%
1 hour	92	90	80	87%
1–24 hours	73	70	54	74%
1–7 days	39	34	23	59%
7 days	41	26	7	17%
No record	2	2	1	
	276	250	190	69%

Duration of P.T.A.—This analysis in Table I is concerned with accidental blunt injuries in which the rate of change of velocity to which the skull is subjected probably determines the degree of brain damage (Denny-Brown and Russell, 1941). In gunshot wounds, on the other hand, the brain is often submitted to little acceleration, and as in other penetrating injuries the damage is often quite local. Thus in Table II the

TABLE II.

Duration of Post-Traumatic Amnesia in a consecutive series of surviving "accidental" and gunshot wound cases admitted to a Military Hospital for head injuries.

		Duration of Post-Traumatic Amnesia					
	Total	Nil	< 1 hr.	1–24 hr.	1–7 days	> 7 days	No record
"Accidental" head injury.	1,022	99	208	312	231	167	5
	—	10%	20%	31%	23%	16%	½%
Gunshot wounds of the Brain.	200	64	40	22	42	24	6
	—	32%	20%	11%	21%	12%	3%

duration of P.T.A. is compared in a series of accidental injuries and of gunshot wounds of the head with dural penetration or skull fracture. No less than 32 per cent. of the gunshot wound cases have no amnesia, and this must be due to a failure of many of these missiles (which include small bomb fragments) to concuss the brain as a whole. There is also a remarkably small proportion of cases of gunshot wound with P.T.A. of one to twenty-four hours. This is in striking contrast to the "accidental" group and indicates that when gunshot wounds do cause loss of consciousness the latter is likely to be either of very short or of much prolonged duration. This can probably be explained by the assumption that when such wounds are of sufficient severity to cause severe general commotion the associated brain destruction will ensure by its extent or its complications that the P.T.A. is prolonged.

TABLE III.

Duration of Post-Traumatic Amnesia in a series of surviving cases admitted to hospital in the acute stage and therefore relatively unselected.

		Duration of P.T.A.					
	Total	Nil	< 1 hr.	1–24 hr.	1–7 days	> 7 days	No record
Military Hospital cases	331	34	115	91	45	43	3
Per cent.		10%	35%	27%	14%	13%	1%
Russell's (1932) cases. Edinburgh	184	80		57	47		
		43%		31%	25%		
Gutmann's (1943) cases. Oxford	179	118		39	19	3	
Per cent.	—	66%		22%	11%	2%	

Table III gives the number of cases in the various P.T.A. groups in an unselected series of acute hospital admissions. The cases were admitted to a Military Hospital for Head Injuries, and were those admitted in the acute stage only; they are compared with figures for general hospitals published by one of us (W. R. R.) and also by Gutmann. There is a close similarity between the figures in the first two groups of cases, while those in Gutmann's series have a larger proportion of slight injuries.

It is now generally agreed (Symonds, 1932; Russell, 1932; Greenfield, 1938; Jefferson, 1942) that the disorders of consciousness following head injury are usually dependent on neuronal trauma and are rarely due to vascular complications such as hæmorrhage, œdema or increased intracranial pressure. Study of the duration of amnesias following injury carries us a step further, for this makes it necessary to postulate many degrees of neuronal commotion which, for example, may recover fully in ten minutes or may "feel their way" gradually to recovery in ten days.

Reduction of P.T.A.—Though the duration of P.T.A. is usually more or less permanent and unchanging, there are exceptions. Occasionally it becomes reduced spontaneously as in the following case:

> Fus. R. sustained a head injury on July 19, 1942. On August 4 he had a momentary retrograde amnesia (R.A.) and a P.T.A. of six days with an "island" on the fourth day. Ten weeks after the accident he regained spontaneously another island in the P.T.A., for while sitting quietly in bed he suddenly remembered being on the floor of a moving truck, and this was, in fact, the way he was brought to hospital.

Cases of reduction in P.T.A. under barbiturate hypnosis are described later. These recoveries of things forgotten are reminiscent of hysterical amnesia and yet there is no reason to suppose they are hysterical.

Delayed P.T.A. and lucid interval.—In some few cases of accidental head injury all details of the injury and of events which closely followed it are clearly recalled, but there follows later a period of confusion and amnesia. This can be referred to as *delayed post-traumatic amnesia.* In most cases, especially in gunshot wounds of the brain, the delayed P.T.A. probably indicates that vascular complications of the wound are responsible for the delayed amnesia. 2·5 per cent. of 1,029 cases of accidental head injury had delayed amnesia, while the figure for gunshot wounds of the skull and brain was much higher, being 14 per cent. in 372 cases. In a very few cases of relatively slight injury the short lucid interval seems to correspond with a period of intense stimulation for the patient which may "keep him awake" for a time. For example, a cyclist whose motor-cycle caught fire after the accident remembers trying to put out the fire and

then no more for many hours. Or again an airman after a crash remembered turning off the petrol before his P.T.A. developed. In this type of case the disturbance of consciousness is relatively slight and a strong stimulus may lead to registration of an event so well that it can be subsequently recalled.

The phenomenon of a lucid interval has for long been recognized as a clinical feature in the diagnosis of extradural hæmorrhage. It should be noted, however, that it is only those cases which have little initial concussion which show this well-developed lucid interval before cerebral compression supervenes. It is equally important to note that there may be a lucid interval followed by delayed confusion in the absence of any gross intracranial complication such as hæmorrhage. This is usually easy to distinguish clinically from the progressive stupor and coma of cerebral compression. These slight degrees of delayed confusion appear sometimes to be due to subarachnoid hæmorrhage, or to minute intracerebral hæmorrhages in the brain-stem (Denny-Brown, 1941).

Islands of memory in P.T.A.—The loss of memory for all events during the time covered by the P.T.A. is not always uniformly complete. In some cases islands of memory emerge which are often concerned with special events such as an operation or the visit of a relative. They are liable to appear when confusion is slight and the patient able to converse and behave in a sensible way. In 13 cases showing an early island in the P.T.A. the final duration of amnesia was one to twenty-four hours in 4 cases, one to seven days in 4 cases, and over seven days in 5 cases. In most of these cases of early islands in the P.T.A. the underlying factors are probably the same as in the cases of delayed amnesia already referred to, but the injury being more severe there is immediate loss of consciousness, then partial recovery or lucid interval corresponding to the "island", and then the delayed amnesia due to vascular complications. As with cases of delayed amnesia, the "island" with subsequent deterioration does not usually indicate that a serious degree of cerebral compression is developing. These islands, when they occur, cannot be localized, for they concern an isolated happening unconnected with the normal chain of memories—restricted paramnesias as Bannister and Zangwill (1941) term them. A special occasion may sometimes appear to be responsible for the return of continuous remembering and the end of the P.T.A. The suddenness with which the patient may "come to himself" is often a striking feature, and is of interest in considering the physiology of P.T.A.

Behaviour during period of P.T.A.—During the stages of recovery of consciousness many remarkable abnormalities are observed. In the first

place the patient's behaviour may closely approximate the normal, and many football players have continued the game and have even played well after a head injury, though they subsequently remember nothing of that part of the game which followed the concussion. Their behaviour may be such that their friends notice nothing amiss, but in other instances there is obvious confusion, as for example the football player who after a head injury plays towards the wrong goal.

Similar abnormalities are sometimes observed after epileptic fits, where again the patient's inability to recall his actions is a striking feature. The term *automatic behaviour* is used to describe this condition, but it must be stressed that the term may refer to behaviour which is obviously confused, or on the other hand to behaviour which is outwardly normal and rational, but in which only the loss of recall indicates that a high level of cerebral function is in abeyance.

Conversation during period of P.T.A.—Many interesting aphasic phenomena occur during recovery from concussion, but these will not be considered here. When the patient is still severely confused he may occasionally give information regarding his injury which is subsequently quite forgotten. Burton (1931) has found that this information may be correct, but care must be taken not to be misled by confabulation.

Case of Memory Regarding Accident During Period of Confusion which was Later Forgotten within R.A.: Confabulation and False Accusation.

W. D. (*Case* P 91), an electrician aged 38, had a motor-cycle accident on 8.8.33, while swerving to avoid a dog. There was a laceration in the left frontal region and a linear fracture of the middle fossa of the skull. Two days after the injury he repeatedly said "It was a dog!" He was however quite confused, and gave the date at February, 1933. He gradually became more alert and confabulated aggressively regarding this early memory, and some information probably derived later from his wife. On 16,8.33 he gave the date and place correctly and said he had been in hospital for a week. "I'm supposed to have had a smash up, but it wasn't my fault—dog flew at me and I flew at it—a big black dog with a white spot on its chest. Farmer's son turned on me and smashed me with an instrument in his hand for damaging him. He is getting arrested to-day—plain clothes officer told me he had been arrested—that is one of the charges I have against him. I've the money to fight the case. I can prove what I said. . . . The police have found the instrument, and everything is turning out as I said. Marks on the instrument and everything . . . the dog did not harm me . . it was the man that hurt me . . . etc."

The condition improved steadily and he was discharged home about three weeks after the accident and resumed work two months after leaving hospital. When re-examined on 9.1.34 he had no recollection of his period in hospital except the last four days (P.T.A. sixteen days). The R.A. was two days, and those two days

were a "complete blank". He was quite fit with no headache or giddiness and he considered his work capacity and memory to be as good as ever.

A witness, who was near when the accident occurred, said it was due to his swerving to avoid a large, black dog with white spots belonging to the adjacent farm. The farmer's son accompanied the patient to hospital in the ambulance, but the patient now has no idea even what the farmer's son looks like.

Occasionally the P.T.A. lengthens in the early days after recovery of consciousness as though the memory of events soon after recovery of consciousness is not retained with sufficient firmness for recall at a much later date. Barbiturate hypnosis may facilitate recall as in the following case:

Case of Lengthening P.T.A. Subsequently Reduced by Barbiturate Hypnosis.

SPR. C. had a R.A. of a few seconds. When questioned *seven* hours after the accident his first memory was of being lifted on to a stretcher. From the account of a witness of the accident this was half an hour after it occurred. Then he remembered nothing more until he heard someone saying that he needed two stitches in his lip: this was half an hour later. When questioned again *one week* after the accident, his first memory of being lifted on to a stretcher had gone, and the earliest memory now was someone saying he needed two stitches. The memory of the entire day of the accident was then vague, whereas it had been quite clear at the first examination. A fortnight after the accident his remembrances were unchanged but his memory of the day of the accident had become even more vague, and he could not give a satisfactory account of his medical examination on the day of admission. Under pentothal, however, he remembered being lifted on to the stretcher, and he also remembered an old lady saying: "Lift him carefully; he's badly injured". (This remark was confirmed by the police.) He now remembered part of the journey in the ambulance, but thought he must have gone to sleep for the last part of it, as he remembered nothing more until he was being stitched. His memory of his medical examination on admission remained, however, as vague as before.

"Visions" relative to the injury.—A curious phenomenon which seems allied to those described above is occasionally described by the patient after full recovery of consciousness. This consists of a transient and sometimes repeated "vision" of something seen just before the accident, though events concerning the vision cannot be recalled in the usual way and fall within the R.A.

One of us (Russell, 1935) described a case of head injury in which for a period of one week only after recovering consciousness (P.T.A. twelve hours) the patient frequently had a sudden vision of the huge tyre of a motor lorry bearing down on him. Though the retrograde amnesia was only a few seconds and the injury was actually due to a motor lorry knocking him down he was never able to remember seeing the lorry which in fact could only have been visible to him for a moment before the injury occurred.

We have recently observed similar cases which were investigated under pentothal hypnosis without restoring any memory of the events relative to the hallucination:

DRIVER T.'s first memory on coming round in hospital was of seeing a horse as in a cloud. He had a very clear idea of the horse; it was a brown cob, and he had a side-view of it. It was galloping with its head up, coming from right to left. There was no cart attached to it; he was unaware of any background of road or surrounding scenery or people or noise. He was unaware of being frightened or of any feeling that an accident was about to occur. This vision at once passed and he was aware of two nurses making his bed. He asked them what had happened, and they told him he had had an accident. He then asked them whether it was anything to do with a horse, and they told him they did not know, but that he had already told them that it occurred through a horse. He himself had no recollection of having told them this. This story of the accident has been confirmed: he did collide with a runaway horse.

DRIVER L. (*Case* 15207) was involved in a motor car accident in April, 1944. He was sitting next the driver and has been told that the accident was due to the steering rod breaking. When examined in September, 1944, he had made a good recovery apart from some headache. He had complete R.A. for about twenty minutes, and this amnesia included a special visit by car to a river. The P.T.A. was for three to four days. Under sodium amytal hypnosis five months after the accident he talked freely but no shortening of the R.A. or P.T.A. could be obtained. He did, however, recover an island in the R.A. during which he was sitting in the car reading a letter while they were travelling at about 35 m.p.h. He also thought that he could remember looking up suddenly, but had no recollection of the driver struggling with the steering wheel, nor had he any memory of the visit to the river.

"Visions".—About two weeks after the accident he had his first "vision" and he had six of these in all, of which four were during the two months following the injury. The "visions" consisted of the sudden appearance in his right visual field of a man, and especially the man's arms, struggling with the steering wheel of a car. This "vision" lasted for a few seconds. It only occurred while he was completely at rest both mentally and physically, generally while sitting in an easy chair. On the first two occasions of the "vision" he felt frightened, and his "stomach turned over", but in the more recent attacks he recognized the "vision" and there was no associated emotional reaction to it. He is naturally a visualist and has visual dreams during sleep, but has never seen this "vision" during sleep and has no dreams relative to the accident.

FITTER P. (*Case MRC* 232) (Hooper, McGregor and Nathan 1945) "came round" in hospital two and a half days after his accident. He became vaguely aware of the ward surroundings, but at the same time he seemed to hear a confused jumble of voices, shouts and the noise of brakes being applied; he saw two car lights, and had a vivid impression of being dragged along on his back. These sensations lasted for about two minutes and recurred later with a highly unpleasant and terrifying sensation as an aura to an attack which might have been an epileptic equivalent.

In this case, unlike the first three, a part of the hallucination was clearly remembered as occurring before the injury, for he remembered the screech of brakes and his being struck by a car but could never recall being dragged along the road.

These rare cases suggest that during the period of confusion isolated and dramatic events preceding the injury may be registered and retained which cannot be recalled in the normal way, but only in the form of "vision".

Confabulation.—During the period of confusion following concussion which falls within the P.T.A., speech and behaviour may be so nearly normal that confabulation misleads the unskilled observer. The subject matter for confabulation is usually unconnected with the injury, but in some instances the patient apparently realizes he has had an accident and confabulates with regard to it. This may lead to the patient making false accusations regarding the cause of the injury, as has been reported by Russell (1935) and Symonds (1937). The hallucinations referred to in the last paragraph may play a part in the confabulation in some cases.

The confabulation may be rational and yet the period of abnormality usually falls within the P.T.A. In such cases the mental activity approximates to normality but there is a loss of continuous remembering, and the context of the confabulation is forgotten.

Secondly there are cases in which the confabulation is subsequently remembered, as may occur after alcoholic intoxication or psychosis of Korsakoff's type. In these instances the faculty of continuous remembering has recovered while the confabulation persists, as in the following case:

Case of Prolonged Confusion with Memory of Abnormal Behaviour after Recovery of Full Consciousness.

R. D. (*Case* P 150) had a severe motor-cycle accident on 3.5.31. When seen a few hours later he was stuporose and very restless. On 4.5.31 he was violent and required forcible restraint for several days. His speech was at first meaningless, but gradually he became very talkative, emphasizing all he said with powerful gestures. He talked incessantly of his ability as a sheep-shearer and fisher, and promised money to Sister and Doctor if they would let him go home. This continued until about 23.5.31 when his behaviour and conversation became normal, and he was most apologetic for his abnormal behaviour. He remembered many events during his confusion, especially during the last week. He had a clear recollection of being strapped in bed, refusing medicine and struggling with the nurses. The R.A. was momentary.

When re-examined nine months after, he was back at work and had made an excellent recovery. He was more talkative than before the injury, but said his memory was excellent, except that he had no idea of the number of sheep he counted six hours before the accident. He was driving his motor-cycle as fast as ever.

The abnormality of localization of islands of memory may contribute considerably to confabulation, as in the case of a fitter, who had an accident on October 10, 1941, while walking in Norwich, and who gave his

story on October 28 in such a way that it was clear that though he gave some particulars correctly, he was confusing his injury with an accident near Epsom which he had two years previously. The confusion was clearly due to failure o localize his memories of the more recent injury.

A similar disturbance of localization has been produced by Flescher (1941), by giving schizophrenics various material to remember before electric shock therapy. He was able to show that though much was correctly remembered it was often localized quite incorrectly in time.

Retrograde Amnesia (R.A.)

The curious phenomenon of retrograde amnesia which is so well known in head injury is also found after electric convulsion therapy, status epilepticus, meningitis and acute cerebral anoxia as in hanging, CO poisoning and severe loss of blood. R.A. is for events which occurred before the injury while the patient was still fully conscious. The events occurring during this period were often dramatic and must have been registered by the normally acting sensorium, yet the injury intervenes and these events are thereby prevented from being retained, or if they are retained they cannot be recalled. The clinical features of R.A. present many interesting variations.

Duration of R.A.—The R.A. is in most cases for a few moments only. The motorist remembers approaching the cross-roads, the cyclist remembers losing control on a steep hill, or the window-cleaner remembers losing his balance. This momentary R.A. is observed after injuries of all degrees of severity and presumably has a clear and uniform physiological basis. In cases of prolonged R.A. other factors require consideration.

Table IV.

Duration of P.T.A. and R.A. compared in 1,029 cases of "accidental" head injury (gunshot wounds excluded).

	Duration of P.T.A.						
Duration of R.A.	Nil	< 1 hr	1–24 hr.	1–7 days	>7 days	No record	Total
Nil	99	23	9	2	0	0	133
Under 30 minutes ..	—	178	274	174	80	1	707
Over 30 minutes ..	—	3	16	41	73	0	133
No record	—	4	14	14	15	9	56
Total ...	99	208	313	231	168	10	1,029

In Table IV the R.A. in 1,029 cases is roughly estimated, and compared with the P.T.A. In Table V, fifty consecutive cases from each P.T.A. group have the R.A. recorded in greater detail. These tables indicate how very constant some period of R.A. is in all injuries which disturb consciousness

TABLE V.

Detailed comparison of duration of P.T.A. and R.A. using 50 consecutive cases from each P.T.A. group.

	Duration of Post-Traumatic Amnesia				
Duration of Retrograde Amnesia	< 1 hr.	1–24 hr.	1–7 days	> 7 days	Total
Nil	9	1	1	—	11
1 minute	34	35	15	12	96
1–30 minutes	6	13	21	18	58
½–12 hours	1	1	9	6	17
½–2 days	—	—	3	7	10
2–10 days	—	—	1	6	7
Over 10 days	—	—	—	1	1
Total	50	50	50	50	200

sufficiently to produce even a short P.T.A. These records were made by many observers, and some errors there must be. It is common, for example, in street accidents for the victim to remember being struck by a vehicle but nothing more. His head injury may, however, have been due to his striking the ground a second or two later, and this would be recorded according to our standards as a momentary R.A. Such cases may easily be entered in error as R.A.: nil. However, there is no doubt that certain cases of accidental concussion with a short P.T.A. clearly remember the head injury, and in Table V there are 11 cases of this type in 200 cases. On the other hand in 186 cases of G.S.W., brain or skull, with a definite period of P.T.A., there were no fewer than 65 with no R.A., that is to say the patient remembered his head being struck by the missile.

Case of Accidental Head Injury from a Falling Stone with R.A.: Nil, and P.T.A.: Twenty-four Hours.

A. M. (P 203), a quarryman, was injured by a falling stone, which was about the size of a man's fist. The stone fell from a height of about 60 feet, and striking his head caused a fissure fracture of the skull in the parieto-occipital region. When questioned ten days after the injury he said that he remembered hearing the stone falling, and he ran to get out of the way. Then he remembers clearly a dull, crushing sensation in his ears, but nothing more until he came to himself in hospital twenty-four hours later. He did not remember falling to the ground after being struck, but the ground was soft, so that it is unlikely that he had a second injury while falling.

Accidental Head Injury: P.T.A.: One Hour, R.A.: Nil.

A. M. (MRC 876) was playing goal in a football match. He remembers diving at the feet of the opposing centre forward, and deflecting the ball. He then remembers seeing a boot coming towards his face, then a blinding flash, but has no memory of the impact. He came to himself in hospital over an hour later.

While cases of this type with no R.A. are common in gunshot wounds, they are, as has been shown, uncommon in accidental injuries. In the two

examples given above, however, it is noteworthy that the accident injury was of the type which is likely to cause focal brain injury as there due to a fast moving object striking the skull. They were in some wa herefore, similar to the wounds caused by the high velocity missile.

Absence of R.A.—The absence of R.A. with definite P.T.A. in gunshot wound cases must be connected with the more focal type of injury. Certainly the immediate loss of memory after the wound occurs too quickly for it to be explained on a vascular basis, and these cases must be clearly distinguished from the delayed amnesias already referred to. Perhaps some diaschisis effect causes the disturbance of consciousness and, if so, the memory of the injury is registered and retained before the trans-neuronal shock effect spreads to prevent further remembering.

Shrinkage of R.A.—During the gradual recovery of consciousness, while there is still some confusion, the R.A. is often very long. This may be so marked that the patient gives the date as several years previously with a corresponding reduction in his age. For example a Polish airman, who crashed in 1941, when questioned three weeks later, was still confused and said it was 1936, and when asked about war with Germany replied "We are not ready yet."

A case previously described (Russell, 1935) was that of P. A. S. (P 234), a greenkeeper, aged 22, who was thrown from his motor cycle in August, 1933. There was a bruise in the left frontal region and slight bleeding from the left ear, but no fracture was seen on X-ray examination. A week after the accident he was able to converse sensibly, and the nursing staff considered that he had fully recovered consciousness. When questioned, however, he said that the date was in February 1942, and that he was a schoolboy. He had no recollection of five years spent in Australia, and two years in this country working on a golf course. Two weeks after the injury he remembered the five years spent in Australia, and remembered returning to this country; the past two years were, however, a complete blank as far as his memory was concerned. Three weeks after the injury he returned to the village where he had been working for two years. Everything looked strange, and he had no recollection of ever having been there before. He lost his way on more than one occasion. Still feeling a stranger to the district he returned to work; he was able to do his work satisfactorily, but had difficulty in remembering what he had actually done during the day. About ten weeks after the accident the events of the past two years were gradually recollected and finally he was able to remember everything up to within a few minutes of the accident.

R.A. at First for Six Months—Shrinking to a Few Minutes. P.T.A. Two Months.

Gnr. J. W. T. (MRC 516) was injured in an air-raid on 28.11.40. When first seen he was deeply comatose with flaccid limbs. Recovery of consciousness was very slow, and he did not begin to talk until a month later. On 11.3.41 his mental state was still greatly retarded. The R.A. was for about six months, and he had

no recollection of three months in the Army. He now remembered coming to himself in hospital in January, 1941, when he found two women and a man sitting at his bed. These people told him they were his wife, mother and a close friend. He remembers arguing with them and saying he was not even married, and that he was certain he had never seen the man before. He was now correctly orientated, but was still very uncertain of the main facts concerning himself. He did all intelligence tests badly, and had difficulty in reading. He was very cheerful and friendly.

By 16.4.41, the R.A. had shrunk to a few minutes, and he remembers standing by the guns on the night he was injured, and that a few shells had been fired, but he does not remember any bombs; the P.T.A. was for about two months. He remained popular with the patients, but childish and slow in his movements with periods of irritability. He was invalided in May, 1941, and returned to light manual work in February, 1942. He found his right leg and arm "untrustworthy", and his relatives said he was forgetful and hesitated in his speech.

In one of this group of cases in which the patient, while still slightly confused but orientated, had a dense R.A. of about a year's duration, amytal was given in an attempt to recover the amnesia but without any improvement.

In these cases of slow shrinking R.A., the P.T.A. terminates long before the R.A. shrinks to its final duration. While the R.A. extends over many months or years the patient may, to careful testing, be slightly confused, but he has often recovered sufficiently to have continuous memory and to behave in a rational way.

During this period of shrinking amnesia the patient is unable to recall an important group of memories which, as later recovery shows, were well registered. The recovery occurs not in order of importance but in order of time. Long-past memories are the first to return, and the temporary blocking of relatively recent memory may be so marked that several years of recent life may be entirely eliminated. For a limited time the patient may re-live his childhood, a state of affairs reminiscent of the case of senile dementia.

During recovery the R.A. shrinks at a varying rate to a point where memory of subsequent events ceases abruptly. This usually leaves the duration of R.A. clearly indicated, but this can only be estimated accurately after full recovery of consciousness.

By the time the R.A. has shrunk to a few minutes or less the patient has usually fully recovered consciousness, and indeed a brief R.A. is often an accurate indication of mental normality.

Table V shows the increasing proportion of cases with a permanent long R.A. as the P.T.A. lengthens, though as has been mentioned the R.A. may be very short in severe injuries. In some cases this matter can be explained very simply, for in attempting to estimate the R.A. the

patient who has emerged from a long P.T.A. endeavours to remember events which occurred perhaps over a week previously. Many uninjured individuals are unable to describe what happened a week ago, unless there is some special experience to remind them.

Prolonged R.A.—This simple explanation does not, however, explain the long R.A. in many cases, especially those in which events of importance to the individual were forgotten. It has already been suggested that the common momentary R.A. is due to a physiological effect of the injury which blocks the retention of events seen or heard in the moments before the concussion. Some very different explanation is required for the relatively long R.A. which may be recorded in severe cases with a long P.T.A. In Table V, 14 per cent. of the cases with P.T.A. over seven days reported R.A. of over two days. These periods of R.A. are completely blank to the patient and often cover important events.

An example of important memories lost during an R.A. lasting several days is the following case kindly provided by Sir Charles Symonds:

Flight-Lieutenant T., aged 31, was seen on February 7, 1936. Following a head injury when flying in 1934 he had been posted to ground duties which he had performed inefficiently, and was charged with being unable to account for stores to the value of £100. On examination he was orientated, voluble, facile and dysarthric. He could not retain more than six digits, showed three errors in repeating name, address and flower after five minutes, and failed in simple mental arithmetic. His face was expressionless with weakness of the left facial muscles. There were no other abnormal physical signs.

The head injury occurred in a crash on April 15, 1934, and there was a P.T.A. of twenty-one days. He came to himself in an eight-bedded ward which he describes in considerable detail, and has a consecutive memory of subsequent events. The story of his R.A. is as follows: The injury occurred on a Monday, and he had joined his unit eight days previously on a Sunday. He remembers arriving on the Sunday night and noticing that his room was of a different type from any he had slept in before. He has an isolated memory of firing at a ground target the following day, and of visiting a café sometime on that day, but has no recollection of the subsequent week. During this period he was on flying exercises of a kind he had not done before in an aircraft to which he was accustomed, doing several trips a day. He had studied his log book giving the details of these exercises over and over again in a fruitless attempt to recall the memory of these days. On May 21, 1927, he had had a head injury with a permanent R.A. of fifteen minutes and P.T.A. for three days followed by a headache for several days.

Islands in R.A.—It is clear that severe head injury may have a specific effect on very recently acquired memories, and this will be discussed later. A long R.A. with a P.T.A. of only twenty-four hours is very unusual, but the following case illustrates this:—

Case of R.A. with Islands for Over 24 Hours. P.T.A. 24 Hours. Investigation of R.A. Under Amytal Hypnosis Made Little Alteration.

Cpl. G. W. (MRC 2039) was thrown from his horse on 20.7.41. He came to

himself twenty-four hours later, and his memory thereafter is quite clear. When examined on 22.8.41 his memory of events before the injury was normal up to the morning of the day before the injury (19.7.41). On this day, over twenty-four hours before the injury, he remembers reporting sick at about 9 a.m. with synovitis of the knee. He was excused duties, but remembers little more of that day—he does not even remember leaving the M.I. room. His wife came to meet him that evening, but he has no memory at all of her visit except that he remembers getting into a bus with her, to see her home, and later being at a station near where she was staying. For the day on which the accident occurred he has no memory except one island—he remembers tying up his horse at the gate where his wife was staying, going to the house and being told his wife was out. From 9 a.m. of the previous day, therefore, there was complete amnesia, except for three short islands. When he came to himself on 21.7.41 his first memory was of tying the horse to the gate.

Under the influence of sodium amytal he became sleepy, euphoric and talkative. Repeated attempts were made to reduce the R.A. and P.T.A. or to increase the islands in the R.A., but without success, except that one further island appeared—he now remembered leaving camp on the evening of 19.7.41, and walking with his friend, Bill, past some sentries.

He made a good recovery, and went to a Convalescent Depot on 2.10.31. Eighteen months later he was Category A, and was then serving efficiently in the Middle East.

In most cases of persistently long R.A. the P.T.A. has also been long. The following are typical examples:—

F/O P. S. G. (MRC 2) crashed on 13.11.39. He was demonstrating a low attack on troops which he had done twice, but on the third attack he hit a tree and his crew of one was killed.

When examined in March, 1940, the P.T.A. was for twenty-eight days. His last memory before the injury was meeting an officer on the way to Ipswich, where the flying was to be. This was two days before the injury, and he has no memory at all of what happened during these two days before the crash.

He made a remarkably good recovery, returned to duty in an administrative capacity, and resumed flying duties successfully in January, 1942. He reported that he was very fit in January, 1944.

2/Lt. E. N. W. D. (MRC 357) had a severe motor-cycle accident on 25.9.40. When examined on 23.11.40 the P.T.A. was complete for five days. About a week before the injury he remembers his unit taking up positions on the coast, and this was of course an exciting time with the prospect of invasion. However, his memory of the week before the injury is very vague. He has an indistinct memory of a demonstration and of one day's training a few days before the injury but otherwise his R.A. is dense for one week.

The injury caused some permanent intellectual impairment and personality disorder. He returned to duty, but found himself to be slow and easily muddled. There was permanent anosmia. He was, however, still in the Army in April, 1944, and his general health was satisfactory.

In these cases there is clear inability to recall important events which must previously have been well registered, retained and recalled before the injury. This type of amnesia is obviously different from the R.A. for events occurring a few moments only before an injury. When important events are obliterated from memory after head injury they are usually

for relatively recent happenings. Recent memories are therefore more vulnerable than those that are remote, but it is remarkable that recent memories for important events should be so completely obliterated from memory as they often are. This long R.A. differs from the memory disorders of organic dementias. In both conditions recent memories are lost, but in the traumatic cases the ability to recall events since the injury has recovered well.

In the case of permanent long R.A. the memory loss resembles that which, as has been mentioned, is often observed during recovery from traumatic confusion, before the R.A. has shrunk down to its final length. In both types of case the relative vulnerability of recent memory is very evident. The retention of recent memories is evidently less firmly established and may, as in these last cases, be abolished permanently by the physical effects on the cerebral neurones of a severe head injury.

Association of ideas may assist the reduction of R.A., as in the case of a soldier who, after recovering consciousness, had an R.A. of over an hour—his last memory was setting out on his journey driving a truck in the dark. Some months later at the cinema he was watching the picture of an aeroplane crashing with the appropriate sounds. The patient found this a very upsetting experience, and suddenly the noise brought back to his mind the noise he heard as his truck crashed.

This type of case bears a remarkable resemblance to the behaviour of a repressed complex, in that an experience which had been registered and retained was not recalled except through an association of ideas, and this experience caused an emotional response which was appropriate to the forgotten material.

Effect of Barbiturate Hypnosis on R.A. and P.T.A.

It is obviously important that the possibility of altering the duration of traumatic amnesia under barbiturate hypnosis should be fully investigated, not only to preclude an hysterical factor in certain cases, but to investigate the possibility of using this method to reduce a purely organic amnesia. One of us (P. N.) has investigated 40 cases recovering from head injury under barbiturate hypnosis.

Method.

On admission to hospital the patient's history was taken in the usual way, but special attention was paid to memory of events preceding, during and following the amnesic period. Within the next few days the patient was again interviewed, encouraged to relax and to attempt to describe all events preceding and following the injury. He was then given slowly an

intravenous injection of sodium pentothal during a period of two to three minutes, until having passed through the stage of yawning he was no longer able to react to commands nor could respond to being shaken (the maximum quantity given was 0·5 grammes). He was gradually encouraged to waken by calling his name or being ordered to rouse himself. Having recovered consciousness sufficiently he was repeatedly pressed to recount all he knew of his accident and of the incidents which preceded and followed it. This was continued until he was able to walk back to bed unaided. During the following days or weeks he would be questioned again from time to time. Where possible the evidence was obtained from witnesses in order to check events elicited from the patient.

Results.

From this investigation of 40 cases with barbiturate hypnosis it was quite evident that in the majority no reduction of amnesia could be obtained. Thus in 28 of the 40 cases investigated the R.A. and P.T.A. remained unchanged.

In the remaining 12 cases, however, some additional memory was recovered, though this was sometimes insignificant.

In 3 cases both the R.A. and P.T.A. were reduced.

L/Cpl. S. R.A. reduced from a few seconds to a moment.
P.T.A. reduced from five hours to one hour.
(Hypnosis two months after injury.)

Cpl. B. R.A. reduced from two hours to a moment.
P.T.A. reduced from eighty-six hours to seventy hours.
(Hypnosis seven weeks after injury.)

In 3 cases the R.A. only was reduced while the P.T.A. was unaffected.

L/Cpl. L. R.A. reduced from half an hour to nil.
P.T.A. reduced from forty-eight hours to nil.
(Hypnosis four weeks after injury.)

Cpl. S. R.A. reduced from sixty-five minutes to three minutes.
P.T.A. fifty-two hours—unchanged.
(Hypnosis five weeks after injury.)

Sgt. B. R.A. reduced from twenty minutes to a moment.
P.T.A. ninety-six hours—unchanged except for an island recovered in the partial amnesic period.
(Hypnosis five weeks after injury.)

Sgt. J. R.A. reduced from seven hours to half an hour.
P.T.A. sixteen hours—no change.
(Hypnosis four weeks after injury.)

In 2 cases the P.T.A. was reduced while the R.A. showed no change.

Dvr. E. R.A. half an hour—unchanged.
P.T.A. two days reduced by a few minutes only.
(Hypnosis three weeks after injury.)

In 4 cases the R.A. and P.T.A. were unchanged, but islands of memory during the amnesic period were recovered.

Spr. C. R.A. momentary—unchanged.
P.T.A. one hour reduced to half an hour.
(Hypnosis six weeks after injury.)

Cadet P. R.A. a few seconds—unchanged.
P.T.A. forty-eight hours—unchanged, but two brief islands of memory recovered.
(Hypnosis three weeks after injury.)

Gdm. McN. R.A. about five seconds—unchanged.
P.T.A. fourteen days—unchanged, but several vague and brief islands of memory recovered.
(Hypnosis three months after injury.)

Fus. K. R.A. seven minutes—unchanged.
P.T.A. three weeks—unchanged, but a few islands of memory recovered.
(Hypnosis five months after injury.)

Dvr. S. R.A. twelve hours—unchanged.
P.T.A. eleven days—unchanged, but a few islands of memory recovered for the latter part of the amnesic period.
(Hypnosis six weeks after injury.)

Analysis of the material recovered under pentothal showed nothing in this material to warrant hysterical repression, and indeed the constancy with which the recovered material borders the fringes of the amnesic period makes it seem probable that the memories recovered were only incompletely abolished. They were recorded, but could not be recalled without a special stimulus applied by questioning during hypnosis. The examiner naturally stimulates the association of ideas, and the spontaneous recovery of forgotten items by a later experience has already been described.

These investigations under barbiturate hypnosis therefore provide confirmation of the view that both the R.A. and P.T.A. in most cases is the result of physical effect of injury on brain neurones.

Hysterical R.A.—Cases are described from time to time in fiction in which there is a permanent R.A. for a large part of the whole of previous life. This may be observed during the stages of recovery before confusion is fully resolved, but we have never observed an R.A. to extend over many months permanently except in hysteria or gross traumatic dementia.

Traumatic Amnesia and Traumatic Intellectual Impairment.

In cases in which the P.T.A. exceeds seven days some loss of intellectual capacity is a common permanent disability. In these cases the general blunting of memory may contribute slightly to the loss of memory of

events before the injury. In considering a general traumatic impairment of memory one is presumably studying the same cerebral mechanism which is disturbed so grossly during the period of R.A. and P.T.A., and it is noteworthy that trauma sufficient to cause a long R.A. and long P.T.A. will also, in many instances, lead to a permanent impairment of the faculty of remembering.

Summary and Discussion.

It is naturally important to discuss the significance of the phenomena described above in so far as they may throw light on cerebral mechanisms. In the first place it is clear that traumatic loss of consciousness prevents remembering, and that this inability to remember events persists in most cases until full consciousness has returned. In other words, the recovery of continuous remembering coincides with a late, if not a last, stage in recovering consciousness.

It may also be affirmed that a single blow of varying severity can disturb remembering, as it does consciousness, for very varying periods of time, and that the duration of this period depends usually on the severity of the initial neuronal commotion.

The almost constant occurrence of R.A. indicates that the injury, though it cannot have time to prevent what is last seen or heard from reaching the sensorium, does completely prevent its retention for future recall. The latter process presumably requires a few seconds of time for completion.

The occasional occurrence of a vision of events within the R.A. indicates that in these cases some form of registration has occurred with great vividness which, though it can never be properly retained for later recall, can reproduce itself from a relatively low level in the form of a momentary "vision." This appears to be a striking illustration of different levels of activity in the Hughings Jackson sense. The injury in such a case appears to have blocked the process of retention half-way.

The variations in the R.A. during recovery of full consciousness seem to be specially significant. Distant memories return first and loss of memories for the previous few years may, for a time, be so complete that the patient believes himself to be several years younger. After severe injuries there may be a permanent R.A. of several days' duration which may include events of great importance to the patient.

General brain trauma therefore has an effect on *recent* memory which is much greater than its effect on remote memory, and this fact must be

closely linked with the physiology of remembering. It is clear that the events forgotten are often of importance to the individual, yet for a time, and sometimes permanently, they are completely erased, while distant memories of little importance are returning freely.

The recovery of this type of memory loss is by shrinkage towards the present time. The long amnestic period recovers not so much according to the relative importance of events forgotten as according to the time before the injury that the events occurred. There is thus a vulnerability of memories which depends directly on their nearness to the injury.

We are thus forced to the conclusion that as memories become older they become more strongly established irrespective of their importance to the individual, while recent memories are relatively liable to traumatic extinction, however important they may be.

Further it is clear that a long R.A. is almost always associated with a long P.T.A. We have good evidence that a long P.T.A. usually means a very severe injury, hence a long R.A. is observed when severe general neuronal commotion has occurred. It can thus be concluded that a long R.A., whether temporary or permanent, occurs after severe neuronal commotion, and that severe neuronal commotion has a much more damaging effect on erasing recent than remote memories.

In the cases with long R.A. which recover spontaneously it is evident that the effect of this neuronal commotion is reversible, but in some cases the effect is permanent.

In either case the observation demands a physiological explanation. It seems likely that memory of events is not a static process. If it were, then distant memories would surely fade gradually and would be the more vulnerable to the effects of injury. On the contrary, when the brain is injured, these distant memories are the least vulnerable. It seems that the mere existence of the brain as a functioning organ must strengthen the roots of distant memories. The normal activity of the brain must steadily strengthen distant memories so that with the passage of time these become less vulnerable to the effects of head injury.

The patient with senile dementia may show a very similar loss of recent memory. She may forget the visit of her favourite grandchild within twenty minutes, yet she remembers an unimportant escapade of fifty years before in every detail. The distant memory shows no sign of fading and this suggests that it has received continual reinforcement and has survived not because it was important but because the brain throughout the decades has strengthened it automatically till it has become highly resistant to cerebral degeneration.

It is tempting to speculate on the possible physiological processes concerned in remembering which could behave in this way. The brain works through chains and circuits of neurones which can set a pattern for automatic responses of infinite variety. Presumably the synapses of such a chain pattern are "opened" to allow the least possible delay and to avoid diversions in other directions. The neuronal system concerned with a certain memory, if it is to behave with the passing of years in the way it does, must then be automatically strengthened or more strongly canalized by the normal activity of the brain, and perhaps indeed this facilitation of the circuit is carried out by the spontaneous rhythm of the neurones concerned.

The recall under barbiturate hypnosis, or occasionally in the state of traumatic confusion, of events which cannot be remembered in the normal state of consciousness is of considerable interest. It seems as if under certain conditions clinically manifest as clouded consciousness, and physiologically determined by impairment of function at Jackson's highest level, pathological recall may occur as a release phenomenon. The twilight states of dreaming and toxic or infective delirium are analogous, and in these also there may be recall of experience not available in the state of clear consciousness.

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THE PUPILLO-CONSTRICTOR PATHWAY AND THE NERVES TO THE OCULAR MUSCLES IN MAN.

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THOUGH the behaviour of the pupil ranks high as a measure of oculomotor nerve function no information is available concerning the intraneural distribution of the pupillo-constrictor fibres between the midbrain and the point where they leave the branch to the inferior oblique muscle on their way to the ciliary ganglion. The present inquiry was undertaken to obtain this information. During the course of the investigation additional observations were made on the structure of the ocular nerves. Nathan and Turner (1942) have suggested that there are two efferent pathways for pupillary contraction—one passing through the ciliary ganglion and subserving the light reflex and the second, subserving the accommodation convergence reflex. Concerning the route taken by the latter they state: "We have no positive evidence of any route, except that passing through the ciliary ganglion." This paper is concerned solely with fibres passing to the ciliary ganglion and these will be referred to throughout the text as pupillary fibres.

MATERIAL.

(*a*) A dissection was made of the contents of four orbits in dissecting-room subjects and the course of the ocular nerves was followed from the brain-stem to their destination. The nerves, internal carotid artery, ocular muscles and ciliary ganglion were then removed *en masse* and the individual structures suitably marked and arranged to permit their identification in section. This tissue was fixed, embedded and serially sectioned at 25 μ. The sections were stained with eosin and hæmatoxylin, drawn on an enlarger and the diagrams assembled to reconstruct the macroscopic arrangement.

(*b*) Fifteen dissections of the orbit and cavernous sinus were examined, particular attention being directed to (i) the course and communications of the nerves in the sinus; and (ii) the possibility of ascertaining by micro-dissection for what distance the terminal branches and the

superior and inferior divisions of the oculomotor nerve could be traced proximally as independent fibre systems.

(*c*) Eight fresh post-mortem specimens of the oculomotor, trochlear and abducent nerves were fixed in Flemming's solution, embedded, serially sectioned at 5 μ and stained with iron hæmatoxylin and light green.

Observations.

Oculomotor nerve.—The nerve was delicately attached to the mid-brain by a series of horizontally arranged rootlets which were soon collected into a single bundle with a thin perineurial layer and a few fine intrafunicular septa. After travelling some distance in the dural wall of the cavernous sinus, this funiculus was intersected by numerous thick, irregular fibrous septa from the dura thereby causing the formation of several irregularly anastomosing bundles which, however, bore no relation to the terminal branching. The presence of this fibrous tissue added considerably to the diameter of the nerve so that it was thicker in this part of its course than elsewhere—this thickness was never due to the addition of other nerve fibres. The fibres were then re-collected into a single bundle which commenced to divide as the nerve approached the lesser wing of the sphenoid. The superior division was formed by bundles separating from the periphery of the upper two-thirds of the nerve; these occasionally formed a crescent over that portion destined to become the inferior division. There was no regular method by which the latter separated into its three branches. Any branch might be formed by several smaller funiculi separating from different aspects of the inferior division or it might arise and persist as a single funiculus.

Traced centrally, the fibres of the terminal muscular branches intermingled soon after joining their respective divisions. The divisions could be traced as independent systems to the middle of the sinus—the fibres of the superior division being arranged above those of the inferior. The neighbouring fibres of the two systems then commenced to interlace and this, together with the complex pattern of the fibrous septa, prevented any further discrete separation of the two divisions. Despite the intermingling of fibres which continued within the single bundle outlined behind the sinus, the superior division fibres appeared to predominate supero-laterally and the remainder infero-medially as far posteriorly as the posterior clinoid process. So far as could be detected by the methods employed all traces of localization were lost behind the clinoid process.

According to Gaskell (1889) the nerve, in the dog, is composed of large (14·4 to 18 μ) and small (3 to 5 μ) myelinated fibres which separate anteriorly

so that the large pass to the muscles and the small to the ciliary ganglion. His only reference to any localization is that just proximal to the ganglion "great numbers of the smallest fibres are seen coming to the periphery of the nerve preparatory to entering the oculomotor ganglion." Barratt (1901) described large (11 to 15 μ) and small (3 to 5 μ) myelinated fibres in the ratio of 3 to 1. Both types were seen in "the various branches of the upper and lower divisions" while the root of the ciliary ganglion consisted chiefly of fibres 3 μ in diameter. He made no reference to the disposition of the fibres of varying diameter within the nerve. Carpenter (1906) reported fibres in the chick varying in diameter from 3 to 15 μ. He said that the oculomotor trunk was composed of the large variety with a few scattered small fibres while there was a zone of the latter about the periphery which passed to the ciliary ganglion. Koch (1916) described large (12 to 16 μ) and small (3 to 6 μ) fibres in the dog in the ratio of 3 to 1 and confirmed the grouping of the small fibres at the periphery reported by Carpenter (1906). He observed that some small fibres did not pass to the ciliary ganglion but he did not indicate their destination. Nakanishi (1924) described fibres ranging in diameter from 3 to 17 μ entering the ocular muscles (sheep and cat): the relative number of the fibres of different size was said to be "not very different but the 3 to 6 μ fibres are rather fewer than either the 6·5 to 10·5 μ or 11 to 17 μ fibres."

The nerves examined in the present study were composed of myelinated fibres ranging in diameter from 3 to 18 μ. A count was made of the fibres of different diameters around the periphery and about the centre of the nerve at several levels. The percentage distribution is given of the fibres in the two regions in a section towards the brain stem (Table I). This arrangement did not alter significantly as the nerve

TABLE I.—PERCENTAGE DISTRIBUTION OF FIBRES OF DIFFERENT DIAMETERS IN THE OCULAR NERVES.

		Region					
		Periphery			*Central*		
		Small	*Medium*	*Large*	*Small*	*Medium*	*Large*
Nerve		3 *to* 6 μ	6 *to* 12 μ	12 *to* 18 μ	3 *to* 6 μ	6 *to* 12 μ	12 *to* 18 μ
Oculomotor	Zone a	48	50	2	21	67	12
	Zone b	28	67	5			
Trochlear		18	69	13	22	64	14
Abducent		17	70	13	20	65	15

was traced forwards. The small fibres predominated at the periphery where there was a further concentration over the superior arc of the

nerve (zone "a" in Table I) where the small fibres were approximately twice as numerous as inferiorly (zone "b" in Table I). These features are illustrated in fig. 1, Plate XXXIV. The small peripheral fibres, within each zone, were evenly distributed either singly or in small clumps of up to 30 fibres. Fibres of all diameters were observed passing into each muscle innervated by the nerve while those passing to the ciliary ganglion were of the finely myelinated variety (3 to 5 μ). The significance of this observation in connection with the localization of the pupilloconstrictor fibres will be referred to again.

The vestigial tissue and the related ganglion cells previously reported at the root of the nerve in man (Thomsen, 1887; Gaskell, 1889; Barratt, 1901; Kopsch, 1907; and Nicholson, 1924) and in various subhuman forms (Tozer, 1912; Nicholls, 1915; McLean, 1926; and Clark, 1926) were observed in two specimens only (fig. 2). There were five ganglion cells in one and one in another. They were situated among the finely myelinated fibres and resembled those comprising the ciliary ganglion. Their morphological features supported the belief (Clark, 1926) that they are aberrant parasympathetic cells and are not representatives of either dorsal (Gaskell, 1889) or ventral root ganglia.

The nerve is described in textbooks of anatomy as communicating, in its course in the sinus wall, with the ophthalmic nerve (*see also* Stibbe, 1930) and the internal carotid sympathetic plexus. Minute bundles of sympathetic and of somatic fibres approximated to the oculomotor nerve in the sinus wall but there was never any communication or exchange of fibres with the latter. No communications were detected by Barratt (1901), Carpenter (1906) and Koch (1916). The experimental work of Tozer and Sherrington (1910) provides evidence that fibres do not reach the oculomotor nerve from the trigeminal.

The pupillary fibres.—The pupillary fibres emerged from the nerve to the inferior oblique muscle in 1 to 3 twigs which proceeded to the ganglion with or without branching. Ganglion cells were observed in these branches; though they were usually localized at the site of entry into the ganglion, in some cases they extended along the oculomotor pathway as far centrally as the superior orbital fissure. Ganglion cells also extended peripherally for variable distances along the efferent ciliary nerves. Ectopic ganglion cells were also reported by Barratt (1901).

Before fusing with the somatic fibres the pupillary fibres, in 1 to 3 bundles, proceeded centrally along the surface of the oculomotor pathway for a variable distance between the superior orbital fissure and their point of entry into the branch to the inferior oblique muscle. Shortly after

fusion the pupillary fibres commenced to scatter, and the intermingling of these and the somatic fibres soon reached a degree which made it impossible to trace them further with any certainty. The identification of pupillary fibres then rested solely on their small size and fine myelination, though to add to the difficulties of interpretation these same features were present in some of the fibres passing to muscle. In the inferior division, the finely myelinated fibres were more numerous at the periphery.

In one specimen, one of two bundles of pupillary fibres proceeded centrally in the manner just described. The second proceeded along the upper surface of the branch to the inferior oblique and the inferior division as far centrally as the superior orbital fissure where it passed to the lateral side of the superior division. It continued independently along the latter for a short distance before joining and blending with its fibres which were, by this time, contained within the main trunk of the oculomotor nerve.

When the somatic fibres of the two divisions had commenced to interlace, the small fibres participated in the process. It may be inferred, however, that the majority of the pupillary fibres would remain in association with the inferior division fibres so long as the predominant localization of somatic fibres was retained. On tracing the nerve back through the wall of the sinus it was subdivided by fibrous partitions and then reconstituted into a single funiculus in which the small fibres assumed a characteristic arrangement which was preserved until the mid-brain was reached. The small fibres were far more numerous at the periphery, where there was a further concentration over the superior arc of the nerve. Details relating to the extent of this concentration are provided in Table I; there were approximately twice as many small fibres in the superior arc of the periphery as in the inferior. Though there was no conclusive proof that the majority of the small fibres in the superior arc were from the ciliary ganglion, circumstantial evidence to support this assumption was provided by three observations: (i) The central portion of each of the three ocular nerves contained approximately the same number of small fibres; (ii) there was no concentration of small fibres at the periphery of the trochlear and abducent nerves as in the oculomotor, and (iii) the number of small fibres was proportionately much greater over the superior arc of the oculomotor nerve than over the inferior. That some of the latter also were from the ciliary ganglion is, however, suggested by a comparison with the trochlear and abducent nerves in which small fibres (all somatic) were slightly less numerous than in the inferior

peripheral arc of the oculomotor. On the other hand, if the oculomotor nerve contains a greater percentage of small somatic fibres than the others, this would account for the slight excess in favour of the part of the oculomotor nerve which is under consideration.

Thus, in the orbit and anteriorly in the sinus, the pupillary fibres may be distributed among the somatic fibres of the inferior division of the nerve or they may occupy a superficial, independent and sharply localized position as far as the superior orbital fissure. Some fibres, however, may be associated anteriorly in the sinus with superior division fibres. Between the middle of the sinus and the brain-stem, it may be assumed that the pupillary fibres become concentrated at and around the superior surface of the nerve. Barratt (1901) does not refer to any localization of the pupillary fibres in his text, but in his illustrations shows them pursuing a sharply-localized course, just inside the periphery of the inferior division, as far centrally as the brain-stem. From his material, methods of investigation and the contents of his text, it is apparent that the cross-hatched areas in his diagrams, representing the pupillary fibres, were so marked on the assumption that the fibres *did* pursue a localized course in the nerve as a discrete bundle.

Trochlear and abducent nerves.—The rootlets of origin of the trochlear nerve quickly merged into a single, compact funiculus with a fine perineurium while the union of the abducent rootlets to form a similar bundle was delayed until the nerve had reached the dura of the posterior cranial fossa.

Though there was, in the wall of the cavernous sinus, a slight degree of partitioning of the trochlear nerve by dural septa the nerve could be considered as a single funiculus until its division just prior to entering the superior oblique muscle. After entering the lumen of the sinus the single abducent funiculus, like the oculomotor, was split into irregular anastomosing bundles by thick septa from the fibrous dural prolongation which accompanied the nerve into the sinus. These bundles fused anteriorly and the nerve continued as a single funiculus until its final division at the lateral rectus muscle.

Contrary to accepted anatomical descriptions (textbooks of anatomy, Stibbe, 1930) there was no exchange of fibres between the trochlear and ophthalmic nerves though they were intimately related in the sinus wall. No communicating branches were seen by Koch (1916). Pearson (1943) wrote: "The part of the trochlear nerve peripheral to the place where it crosses the ophthalmic nerve is larger than the part of the nerve at its exit from the brain." He interpreted this as evidence that the

trigeminal nerve contributed fibres to the fourth. This study has shown that any increase in the size is due to fibrous and not nerve-fibre additions. Some sympathetic fibres from the carotid plexus accompanied this nerve for part of its course in the sinus wall but there was no exchange of fibres.

Barratt (1901) observed that the abducent nerve was joined by fibres which later left it. He stated that these probably represented the communicating twigs which textbooks of anatomy describe as passing to the carotid plexus and to the ophthalmic nerve. Stibbe (1930) reported a communication which, he believed, carried fibres from the ophthalmic to the abducent nerve. The present findings demonstrate that these twigs are sympathetic in origin and are temporarily related to the abducent nerve as they pass from the carotid plexus to the ophthalmic and maxillary nerves.

The abducent nerve was regularly joined by a large branch, composed of several funiculi from the carotid sympathetic plexus, which accompanied the nerve for a short distance before leaving it and dividing into branches for the maxillary and ophthalmic nerves. In most specimens this branch could be easily separated by dissection from the abducent nerve without any apparent exchange of fibres—a loose non-communicating union was confirmed histologically. Examination of the histological material also provided an explanation of the inability to effect such a separation in other specimens. In these cases the sympathetic bundles and the abducent funiculus were involved simultaneously in the fibrous partitioning which bound the two tightly together. Despite this intimate relationship there was no intermingling of the two separate bundle systems nor was there any obvious exchange of fibres at points of contact. While it was impossible in some cases to exclude the possibility that some sympathetic fibres had passed to the abducent nerve it was certain that none passed in the reverse direction. The arrangement was such that if any passage of sympathetic fibres did occur it could not have involved more than 30 fibres. No other communications were observed. Koch (1916) traced sympathetic fibres to the nerve in the cavernous sinus; the main group of these left the nerve further distally to pursue an independent course but their destination was not given.

Large, medium and small fibres were observed in the trochlear and abducent nerves and fibres of all diameters were traced into the muscles. The percentage distribution of fibres of varying diameter about the centre and at the periphery of the nerves is shown in Table I. The finely myelinated fibres in both were evenly distributed throughout both nerves

and were proportionately less numerous than in the peripheral field of the oculomotor. Gaskell (1889) described large fibres (14·4 to 18 μ) in both nerves and small fibres (3·6 to 5·4 μ) in the trochlear while there were in comparison very few small fibres in the abducent nerve; no ratios were given. In the trochlear, Barratt (1901) described large (12 to 19 μ) and small (4 μ) fibres in the ratio of 3 to 1; the fibres in the abducent were said to range from 3 to 6 μ for the smallest fibres and from 11 to 17 μ for the largest but no ratios were given. In Koch's (1916) preparations all three ocular nerves were said to show "strikingly similar characteristics as to the size of the fibres and the ratio of the small and large fibres." The peculiar vestigial tissue and ganglion cells among the rootlets of the trochlear and/or abducent nerves reported by Thomsen (1887), Gaskell (1889), Barratt (1901), Tozer (1912), Nicholson (1924) and McLean (1926) were observed but not investigated.

Ganglion cells in the internal carotid plexus.—The presence of ganglion cells in the internal carotid plexus, originally reported by Krause (1882) and more fully described by Gellért (1934), was confirmed. They presented the features recorded by Gellért and will not be further discussed. They are sympathetic cells and, when considering the effects of extirpation of the superior cervical sympathetic ganglion, their existence should not be forgotten.

Summary.

(1) An anatomical study has been made of the ocular nerves with particular reference to the pupillo-constrictor pathway.

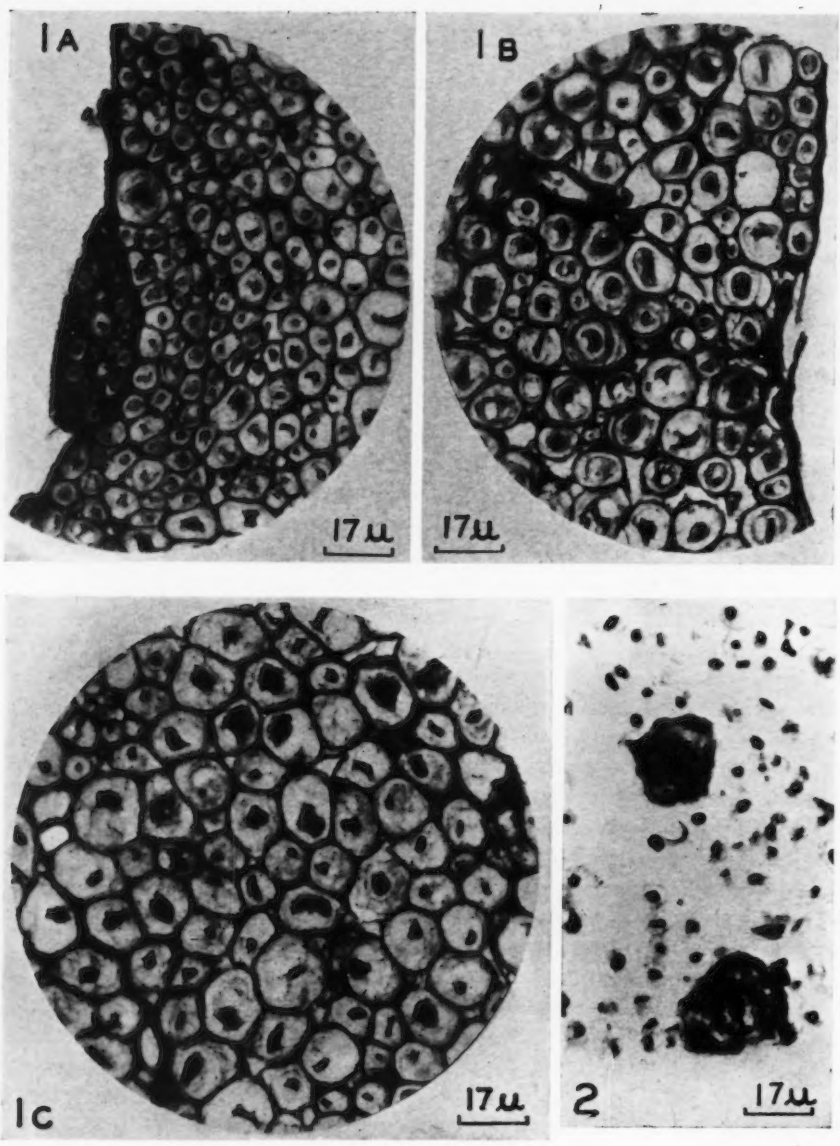
(2) In the orbit and anterior part of the cavernous sinus the pupillary fibres may be distributed among the somatic fibres of the inferior division of the nerve; or they may occupy a superficial, independent and sharply localized position as far as the superior orbital fissure. In the front part of the sinus, however, some fibres may be associated with superior division fibres. Between the middle of the sinus and the brain-stem, it may be assumed that the pupillary fibres become concentrated at and around the superior surface of the nerve.

(3) Observations were made on the degree of myelination of the various fibres comprising the nerves to the ocular muscles, and on the communications between these and other nerves in the region of the cavernous sinus.

(4) The presence of a sympathetic ganglion on the internal carotid plexus has been confirmed.

(5) These observations are important for an understanding of: (i) the pupillary signs accompanying basal lesions; (ii) proprioceptor activity as

PLATE XXXIV



To illustrate article by S. Sunderland and E. S. R. Hughes.

it affects the ocular muscles; and (iii) the effects of extirpation of the superior cervical sympathetic ganglion in experimental investigations into the distribution of the sympathetic fibres to the head.

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PLATE XXXIV.

FIG. 1.—Photomicrographs (to the same magnification) illustrating the distribution of the fibres of different diameters in the oculomotor nerve: (A) zone "a": superior surface; (B) zone "b": inferior surface; (C) central.

FIG. 2.—Neurons in the root of the oculomotor nerve.

"INJURY ACTIVITY" AND "TRIGGER ZONES" IN HUMAN NERVES.

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Introduction.

For many neurologists, the nerve fibre, even under pathological conditions, is merely a well-insulated cable, conducting impulses from one point to another. If its conductivity is broken phenomena arise which can be ranged in the large clinical group, symptoms of deficiency. This view, however, proves to be inadequate to explain some phenomena from another large clinical group, symptoms of irritation (*see* e.g. Riddoch, 1938, and Martin, 1945). Paresthesias (Lewis, Pickering and Rothschild (1931), Zotterman (1933), Kugelberg (1943, 1944)), muscular fasciculation, spasms (Kugelberg, 1944, 1945), as well as pain in certain circumstances have their origin in nerve fibres.

It was well known to classical neurophysiology that impulses may be discharged from injured regions of a nerve. With modern neurophysiological methods Adrian (1930) studied the discharge of impulses from the injured end of mammalian nerve. He found that three different types of discharges might occur. One consisted of a regular continuous series of impulses of high frequency, over 150 per second, which, if the frequency diminished, passed into the second type, with irregular impulses of relatively low frequency. The third type was characterized by groups of discharges, each group consisting of impulses with high frequency, but each individual group recurring with low frequency, 5 to 20 per second. The cause of the activity might be considered to be the injury current which is sufficiently strong to act as a stimulus. Adrian moreover showed, as was likewise observed by Skoglund (1942), that severance of sensory nerves produces greater activity than that of motor nerves.

In man, various symptoms of local irritation in nerves can be produced by compression ischemia. By following the changes in electric excitability in nerve in terms of rheobase and accommodation during and after ischæmia, I have (1943, 1944, 1945) been able to define some of the con-

ditions under which an active focus in the nerve gives rise to spontaneous discharges. The results of the measurements of such parameters of excitability are in good conformity with those obtained, on excised frog nerve, by Solandt (1936), Katz (1937), Schriever and Cebulla (1938), as well as by Lehmann (1937) on mammalian nerve *in vitro*.

The object of the present work is to analyse by electromyography discharging foci and "trigger zones" in nerves. Since these were produced by compression ischæmia, it is necessary to begin with a description of this technique and the phenomena elicited by the ischæmia.

If a pneumatic cuff is distended until the systolic pressure on the arm is overcome, the rheobase, as measured on motor and tactile fibres, is lowered even after a few seconds of ischæmia. After the lapse of a minute or so, one feels a vibrating sensation in the hand, due to the fact that fibres transmitting light touch are beginning to discharge. The discharge is caused by the increase in excitability, which reaches its maximum when the paresthesia culminates two to five minutes after the commencement of the ischæmia. The excitability then diminishes and the tactile paresthesia is abolished.

If the pneumatic cuff has been kept on for a sufficient length of time, the same process is repeated on its removal. The excitability again rises, and it may be added that the accommodation in the motor nerve fibres is completely broken down. The nerve again begins to discharge. One feels a paresthesia, but of a somewhat different nature than that first mentioned. It is this paresthesia that we feel when a leg or an arm which has "gone to sleep" returns to its normal state. When the excitability has again diminished and the accommodation is improved, the paresthesia ceases.

Normally, activity in motor fibres is obtained merely in isolated cases during ischæmia, and afterwards only if the pneumatic cuff has been kept on for a long time, about half an hour, which is unpleasant. The investigation of motor impulses, however, can be facilitated by reducing the amount of ionized calcium in the blood, e.g. by hyperventilation. Such reduction, in fact, enhances the excitability of the nerve, i.e. lowers rheobase and accommodation, and this increase of excitability is superadded to that during and after ischæmia, so that the critical value is reached when also motor fibres begin to discharge. Conversely, an increase of calcium reduces the excitability, thus counteracting the enhanced excitability during and after ischemia, with the result that no activity is obtained (Kugelberg, 1944, 1945). With these methods, the intensity and distribution of the activity in the nerve fibres can be regulated as required, so that facilities are afforded for its study.

Technique.

For the study of the impulse activity *during* ischæmia, the experimental subject was caused to hyperventilate for a few minutes before a pneumatic cuff was laid on the upper arm and distended over the systolic pressure. In order to study the activity *after* ischemia, the pneumatic cuff was kept on for fifteen to twenty minutes, and the subject was caused to hyperventilate for a minute or so before and after the cuff had been removed. With the technique adopted (*see* Kugelberg, 1944) it was ascertained that the activity had really come from the nerve, and not from the muscle, end-plates or nerve endings.

The activity in the nerve was recorded indirectly as action potentials in the 1st dorsal interosseus muscle with the concentric needle electrodes of Adrian and Bronk

(1929). The impulses were recorded with a condenser-coupled amplifier and a cathode-ray oscillograph.

When electric stimulation was adopted, the stimulating electrode (the cathode) was applied at the "nerve point" over the ulnar nerve, either at the wrist, the elbow-joint or the axilla. Monopolar stimulation was mostly employed.

In order to diminish shock artefacts, the experimental subject was "earthed" at a point as close to the recording electrode as possible. The stimulating electrodes were fixed with strips of adhesive tape. For shock excitation, a thyratron stimulator with variable frequency was employed. In order to avoid distortion of the stimulating current owing to the high skin-resistance and changes in it due to polarization, etc., the current passed through an amplifier with a high internal resistance (100,000 ohms). The same procedure was adopted for stimulation with constant current.

In some tests with electric shocks, the stimulating current was at the same time caused to start the sweep of the cathode-ray oscillograph, which had been suppressed. Thus, the beam is immediately started by the shock and is carried horizontally over the screen once for each shock. When the film is running vertically in front of the beam a series of pictures are obtained. Each picture shows, on the left side, the moment of stimulation on the starting of the beam, often marked by a shock artefact, and then, after a shorter or longer interval, the muscular activity caused by the shock. The other beam of the oscillograph was connected to an oscillator which records the time in milliseconds or 1/100th seconds

Results.

Spike Activity During *Local Ischæmia.*

General characteristics.—When the pneumatic cuff has been applied, the rheobase is rapidly lowered. After a minute or so, spontaneous activity appears in motor fibres; after the lapse of a few additional minutes, the activity subsides according as the rheobase rises (cf. Kugelberg, 1945).

The motor effect first consists of irregular twitches in a fascicle. These gradually develop into a tetanus. The records have been taken at a moment when merely a few fascicles have been in activity.

In order to avoid the occurrence of the Trousseau phenomenon when the pneumatic cuff is distended, the preceding hyperventilation was restricted to a few minutes. The motor effect in the Trousseau phenomenon is a continuous contraction of the small hand-muscles, similar to the voluntary contraction. The impulse activity was found to consist in single or, mostly, double spikes (more rarely of triple spikes) with a frequency of 7 to 16 per second, with a machine-like regularity. This activity, which seems to correspond closely to the grouped discharge, is being subjected to further analysis.

As the Trousseau phenomenon *may* be a reflex (*see* Kugelberg, 1945), though my subsequent tests have shown this to be improbable, it has in this connection been regarded as a source of error. The present investiga-

tion is thus confined to an analysis of discharges which give rise to irregular contractions in small isolated fascicles.

The impulses recorded in fig. 1 consist of isolated action potentials of the same appearance as ordinary muscle action potentials in voluntary contraction. They start at low frequency and are then very irregular. The frequency is usually about 20, the highest recorded being 80 per second. When the frequency has reached its culmination it again diminishes and the potentials come more irregularly. This type may correspond to Adrian's type 2. It attains considerably higher frequencies than the individual "bursts" in the group discharges (*see* next section) and will therefore have a different effect on the normal transmission of impulses in the nerve fibre (analysed below).

Effect of spontaneous activity on the physiological transmission of impulses in the nerve fibre and vice versa.—It is evident that the pathological activity will give rise to different symptoms of irritation according to the fibre system in which it originates. It is equally evident that it must also produce symptoms of deficiency owing to the fact that the nerve fibre is then more or less blocked by impulses which proceed in both directions (antidromically and orthodromically) from an active focus. An attempt will now be made to analyse this blocking effect.

If two impulses collide, they will extinguish one another. The nerve fibre would therefore be completely blocked if the frequency of the spontaneous impulses relatively to its length and rate of conductivity were so high that an impulse is always on the way in an antidromic direction in the nerve fibre before the normally conducted impulse has passed. However, the antidromic impulses do not operate in this way when they abolish the physiological function.

The voluntary background activity in a muscle is extinguished for a time, the so-called "silent period," by a stretch reflex (such as the knee-jerk), as was first shown by Hoffman (1919) in man and afterwards confirmed, e.g. by Lindsley (1934). In studies on cats, it has also been shown by Denny-Brown's (1929) method of backfiring (Eccles and Hoff (1932), Hoff, Hoff, Bucy and Pi-Suñer (1934), Hoff, Hoff and Sheehan (1935)) that an antidromic impulse backfired into the anterior horn gives the same effect as if the neuron had been stimulated in the normal direction. The length of the "silent period" depends on the frequency of the impulses in the background activity. The duration of the inhibition will be longest if the antidromic impulse acts very early in the rhythmic cycle of the motor neurons, but will not exceed 1·5 times the interval between two successive impulses, Eccles and Hoff (1932). The frequency of the

voluntary impulses, in the case of a weak contraction, is in man about 5 per second, and usually does not exceed 50 to 60 per second, Smith (1934), Lindsley (1935), Hoefer and Putnam (1939), Seyffarth (1939), etc. This implies that the "silent period" for an antidromic impulse must range between 200 and 20 msec., depending on the degree of contraction.

From this it may be inferred that, if the anterior horn cells are bombarded at a frequency so high that the succeeding impulse will fall within the "silent period" entailed by the immediately preceding one, no voluntary impulses at all will pass through. This should at least occur when the antidromic impulses have a higher frequency than those proceeding from the neuron.

This is exemplified by fig. 2. The ulnar nerve is stimulated with thyratron shocks above the elbow. To the left of the figure (record *a*), we observe a voluntary activity consisting of small impulses. Then the shock excitations are put in, with a frequency of 10 per second. The large spike represents the contraction of the muscle caused by the electrical stimulus. Then follows the reflex response, if any: here, however, it is very slight or missing, succeeded by a "silent period" of about 40 msec.

In record *b* the frequency of excitation has been raised to 30 per second, so that the immediately following shock will fall within the "silent period." The voluntary impulses are now completely inhibited. Even if the voluntary contraction is considerably intensified, all that happens is that the reflex response is facilitated (record *b*, lower curve). It has also been observed that, after iterative excitation the "silent period" is considerably prolonged as compared with its duration after a single shock. The inhibition is additive, just as the subnormality following tetanic excitation of a nerve (Gasser, in Erlanger and Gasser, 1937). It is thus evident that antidromic impulses of relatively moderate frequency seriously disturb the normal function.

The picture, however, would not be complete without regard to the way in which, vice versa, the orthodromic impulses affect an active focus. On account of the shock artefacts an experiment of this nature is not easily conducted with human subjects. The amplification must be relatively high, whilst the shocks must be strong, in order to make sure that the nerve fibres which are spontaneously active have really been excited by the shock. In a few tests, however, successful results have been obtained (fig. 3). The nerve was stimulated at the axilla and the pneumatic cuff, causing the discharging focus, was placed just above the elbow.

The frequency of the spontaneous activity recorded in fig 3*a* is about 16 per second. The frequency of the interpolated shocks (record *b*) is

10 per second. As shown by record *b* the stimuli reduce considerably the spontaneous discharges. A part of this effect may be due to some impulses falling in the refractory periods of the muscle, set up by the shocks. But the diminution in frequency is too great for that. As a matter of fact the total sum of spontaneous and electrically induced impulses is approximately the same as the number of spontaneous impulses before electrical stimulation started. The action potentials which pass through the focus as the result of the shock are followed by a period which is approximately equal in duration to the intervals between the spontaneous impulses during which no new impulses occur. This must be due to the fact that in the focus each impulse elicited by the shock is followed by a period of reduced excitability, which determines the interval to the following spontaneous discharge.

A similar observation in regard to the peripheral nerve was reported by Gasser (1935). He found that a maximal shock excitation inhibited the activity proceeding from the cut surface of cat nerve for a time determined by the subnormal period of the nerve fibres. On the basis of this observation, he demonstrated the marked correspondence between the subnormal period of the nerve and the silent period of the motor neurons.

The occurrence of a "silence period" in the nerve on man can also be strikingly exemplified (*see* fig. 2*c*) by stimulating the nerve at the elbow with a constant current, so that a continuous activity is obtained, and then applying shocks to the nerve at the axilla. As we see, "silent periods" of the same duration as in antidromic excitation of the anterior horns are obtained.

Thus, spontaneous activity as well as that elicited by a constant current reacts to a passing impulse similarly as does the activity from the anterior horn cells. From the special point of view of this study, it shows that a pathological focus can be inhibited just as well as the physiological transmission of impulses. A physiological and a pathological focus may therefore balance one another. Which of them is inhibited depends on relative frequencies, subnormality, and, possibly, on the degree of synchronization. The focus with the faster frequency will inhibit the slower one. This must hold good also for sensory fibres.

Grouped Discharges after *Ischæmia.*

General characteristics.—About one or two minutes *after* the removal of the pneumatic cuff, activity begins in the 1st dorsal interosseus muscle. Its intensity is determined by the duration of the ischæmia and by the hyperventilation and the consequent increase of excitability in the nerve.

In order to avoid the production of tetany symptoms, which would disturb the experimental conditions, hyperventilation was not continued for more than four minutes. The activity culminates within six minutes, when the increase of excitability is at its maximum. The activity may be so intense that the whole bare line on the electromyogram is taken up by action potentials. The motor effect too is rather intense. The small hand muscles contract, and rather slow tetanic, irregular movements are observed on their surface. When the excitability again diminishes, the activity slows down. There are then merely a few fascicular twitches, likewise rather slow, occasionally worm-like. At that stage, the electromyogram can best be analysed.

The recorded activity (fig. 4) consists of groups of discharges of rather low frequency, reminiscent of Adrian's third type of injury discharge. Each individual group consists of closely spaced potentials. When the groups can be separated they are seen to come at regular intervals until they suddenly cease. The lowest regular frequency recorded is one per second. In fig. 4*a*, the frequency at the moment of cessation was about 2 per second for the two different groups. In record *b*, illustrating another experiment, a group starts suddenly with a frequency of about 7 per second, and disappears when the frequency has fallen to about 4 per second.

It should also be pointed out that the recorded activity as a rule does not originate from a single point in the nerve fibre, but from a large segment of the previously ischemic stretch of nerve; chiefly its proximal part, where the increase of irritability is greatest (Kugelberg, 1944). The length of the stretch of nerve that discharges depends on the duration of the ischemia and the hyperventilation. However, if one waits until the activity is about to cease (the moment reproduced in fig. 4) activity is obtained from a particular focus, as shown by the fact that the frequency now has become regular. The lower limit for the frequency of the group discharge can thus be determined correctly.

Fig. 5 presents a detailed analysis of the grouped discharges, recorded with a faster sweep. The number of potentials in the same "burst" varied between 2 and 30. The recorded frequency of the action potentials in each "burst" varied between 100 and 180 per second, so that the interval from the commencement of one potential to that of another is 10 to 5·5 msec. (cf. Adrian's, 1930, values 4 to 10 msec.). Owing to the high frequency the size of the impulses diminishes during a "burst."

The reaction of the hyperexcitable focus to a passing action potential.— If we wait until the excitability in the focus has diminished somewhat, so that the nerve is quiet, and then execute a light voluntary movement

the picture recorded in fig. 6 is obtained. The voluntary spike, which enters the pathologically changed region elicits from it a fresh "burst" containing up to 30 impulses. It has thus acted as the trigger on this "trigger zone" of the nerve. Even a very light contraction leads to greatly multiplied activity (*see* fig. 6, record *a*). After some further time this tendency to respond with grouped discharges diminishes. At this point a most interesting effect can be recorded. If the subject contracts the muscle investigated very slightly, no single voluntary action potentials pass through. Only the characteristic grouped discharges are observed. But, if the contraction is continued with constant strength then single voluntary spikes will soon appear in increasing number (record *b*).

If the muscle contraction is augmented so that the frequency of the action potentials entering the focus in the nerve fibre increases and the trigger mechanism consequently is brought into operation at more frequent intervals it ceases to respond or is inhibited more rapidly.

The reaction of the trigger zone in the nerve to electrical stimulation.— The trigger mechanism and its reaction to electrical stimulation can best be studied during the first few minutes after the cessation of the spontaneous activity, before the rheobase and the accommodation have risen from their low value.

Constant current. The normal electromyographic response to stimulation with slowly rising constant current in man has recently been analysed by Kugelberg and Skoglund (1946*a* and *b*). It is interesting to note that in this manner the voluntary contraction can be imitated. However, the trigger zone in the post-ischæmic region of nerve behaves differently. As shown by fig. 7, the stimulus reactivates the grouped discharges which had previously occurred spontaneously. A similar response to the constant current has been observed by Erlanger and Blair (1936) on frog nerve as well as by Granit and Skoglund (1943) on cat nerve (cut end).

Shock: Stimulation by a condenser shock through an electrode on the intact part of the nerve, proximally to the place where the pneumatic cuff has been applied, discharges an iterative response.

In the case shown in fig. 8, the stimulus was set up at the axilla. It was synchronized with the sweep, so that the beam started at the moment of stimulation and moved horizontally over the screen.

The submaximal synchronized spike which is the response to the stimulus is followed (fig. 8*b* and *c*) by a number of spikes, gradually damping out. The second and third spike is about two-thirds of the first in size, which indicates that a very large fraction of all the excited nerve

fibres iterate. Some records were taken with a faster sweep (fig 8*b*). These show that the trigger zone discharged its first potential 7 to 10 msec. after the passage of the shock, an unexpectedly long latent period but corresponding in duration with the intervals between impulses in a spontaneous burst.

A number of records at a stimulation frequency of 1 per second are shown in fig. 9a. At this low frequency the trigger mechanism is not fatigued. But if we wait a few minutes until the excitability has further diminished, we may find indications of fatigue. In record *b*, the nerve was stimulated at a frequency of 10 per second. The secondary spikes then rapidly diminished in size and number, ceasing almost entirely after about 30 shocks (record *c*). The highest frequency of excitation that the trigger mechanism will stand without evident fatigue lies between 1 to 5 per second, which is the same frequency as that of the spontaneously occurring grouped discharges just before their cessation.

Schaefer and Schmitz (1933) have noted that the contraction of the frog's nerve-muscle preparation increases during local compression of the nerve, an apparently related phenomenon.

The effect of an antidromic volley on the trigger zone.—A single stimulus, e.g. a thyratron shock, applied to the ulnar nerve at the wrist sets up two impulses, one which passes orthodromically or centrifugally and the other antidromically in the excited motor nerve fibres up to the spinal cord.

The antidromic impulse will set up a state of hyperexcitability in the trigger zone which will give rise to a series of new impulses. These impulses, in turn, may be expected to spread not only antidromically together with the impulse, which started them, but also orthodromically. In the latter case they should be recorded as a kind of pseudo-reflex in the hand muscles of the ulnar nerve. This in fact has been found to be the case.

Fig. 10 shows such a test made with the same technique as that described in the preceding section.

In the case illustrated in record *a*, the stimulus was set up at the wrist *before* the nerve was exposed to ischæmia (control). Furthest to the right the moment of stimulation is indicated by the start of the beam. After the lapse of 6·5 msec. follows the response in the 1st dorsal interosseus muscle (the stretch of nerve about 14 cm. from the site of stimulation). After a further interval, in this case after the lapse of 28 msec., a reflex response may sometimes be obtained especially if the experimental subject facilitates it by voluntary contraction (Hoffman, 1934).

In fig. 10, record *b* and *c* the nerve was stimulated *after* the ischæmia.

but when it had become silent. The upper edge of the pneumatic cuff had been placed at a distance of about 42 cm. from the site of stimulation. As shown by record *b*, an iterative response from the focus was obtained 16 to 17 msec. after the direct response of the muscle. This focal response usually consists of large synchronized spikes. A protracted period of asynchronous activity has sometimes been observed to follow the excitation (fig. 10, record *c*). If we know the whole time of the response reflected from the focus, the rate of conduction in the fibres and the interval of time in the focus between the antidromic volley and the focal response that it has elicited, the position of the focus in the nerve can be computed exactly. The interval between the focal response and the moment of antidromic stimulation may be assumed to be identical with the interval between a stimulus to the nerve above the focus (cf. fig. 8*b*) and the "burst" which it elicits.

In this particular case $16-7=9$ msec. are due to the conduction time. The rate of conduction in the nerve was computed by stimulation at the elbow and at the wrist and was found, for the intervening stretch of nerve, to be about 50 m. per second. At this rate, 9 msec. corresponds to 45 cm. whence the focus is at a distance of 22·5 cm. from the stimulating electrode, which is a plausible value.

Fig. 11 illustrates the conditions after repeated stimulations at 1 per sec., record *a*. At this rate little fatigue could be observed. However, if the frequency of excitement was raised to 10 per sec. (record *b*), the "reflex" rapidly became exhausted. At first every other response dropped off, soon afterwards all of them. But, if the nerve was allowed a rest of some tens of seconds the whole procedure could be repeated (record *c*). The focal response behaves in this respect exactly in the same way as when the trigger zone is bombarded in the reverse direction.

Discussion.

This investigation has comprised thick motor fibres. The "spontaneous activity" in these fibres arises when the excitability is raised to a certain critical value, and ceases when the excitability falls below that value (Kugelberg, 1945). It is therefore evident that all interferences which entail changes of threshold in the nerve are bound to affect the intensity of the activity.

It is probable that the ischæmic injury excites the autorhythmic mechanism of the nerve fibre similarly as does excitation with a constant current. The constant current generates afresh the activity which had ceased, whether this is in the nature of "bursts" or of single action poten-

tial discharges. The electrical current and the ischæmic injury may, in some degree, replace one another in bringing about the same effect. The type of effect then depends upon the inherent properties of the nerve fibres. From this point of view, the "burst" is a more pathological type of activity than the single action potential type, which is the reaction of the normal nerve fibre to an excitation.

In order that a constant electric current may be able to maintain a continuous discharge, it must have a strength well exceeding the threshold for rheobasic excitation of the fibre. As the nerve fibre has the capacity of accommodating itself to the excitation, the threshold will throughout be raised, so that the effect of the excitation will be counteracted.

It is therefore reasonable to suppose that the accommodation in the nerve fibre plays a decisive part in the origination of spontaneous activity. That motor excitation phenomena arising in nerve fibres occur so rarely under pathological conditions as compared with sensory phenomena may be explained by the fact that the motor nerve fibres have better accommodation than sensory nerves (Skoglund, 1942, on cats, Kugelberg, 1943 and 1944, on man).

Moreover, on account of the clinical importance of pain, "discharging lesions" and "trigger zones" must be relatively more important in sensory nerves. The choice of motor nerves for this investigation has been motivated by their greater accessibility to quantitative analysis. However, we shall now consider the sensory equivalents to the motor phenomena, the two paresthesias *during* and *after* ischæmia.

During ischæmia a paresthesia develops in the thickest tactile fibres and is felt as a soft, vibratory sensation in the hand, most pronounced on the under side of the fingers and on the palm, where the sense of touch is most developed. Patients who are troubled with this sensation, for example in tetany, usually do not complain about the actual paresthesia, but about numbness.

If the sensitivity to light touch is tested with a piece of cotton-wool at the place where the paresthesia is proceeding, we find that the perception of touch is diminished, which explains the feeling of numbness.

If the place is stimulated more strongly, for example by passing the hand over it, the paresthesia will momentarily disappear. But, immediately after the cessation of the excitation, it will return with greater force, in order after a few moments to recover its original intensity. A continuous touch will at first abolish the paresthesia, but it will afterwards return and slowly increase in intensity (Kugelberg, 1944).

The reduced perception of touch in the paresthesic region can now be explained by the shower of impulses (from the focus) which antidromically block the sense organs (cf. Cattell and Hoagland, 1931) and thus diminish their excitability, in addition to whatever effects the orthodromical impulses elicit in the centres. On the other hand, the disappearance of the paresthesia after a strong stimulus (touch) would be a consequence of the state of depressed focal excitability exemplified in fig. 3 by the effect of passing action potentials on the spontaneous discharge in motor nerve fibres. The rapidly adapting sense organ of touch soon ceases to respond and thus the paresthesia is quickly restored as soon as the discharge from the sense organ is reduced in frequency.

The paresthesia *after* ischæmia is well known as the "pins and needles," investigated e.g. by Lewis, Pickering and Rothschild (1931) and Zotterman (1933). The pricks almost certainly correspond to slow frequency grouped discharges of repetitive impulses. v. Frey (1929) pointed out that the intensity of the paresthetic sensation increased immensely if the corresponding skin area was stimulated. This reaction is simply explained by the excitation of the sensory trigger zone.

Many other sensory phenomena such as hyperalgesias, hyperpathias, *Paracusis Willisiana*, could be profitably discussed from the points of view that these experiments have suggested. But it is hardly worth while to do it now, in the absence of direct evidence from the sensory sphere.

Summary.

The impulse activity from nerve fibres, obtained by experimental reversible injury caused by local ischemia (by compression with cuff), has been studied in man with the aid of electromyography.

Two different forms of spontaneous activity from the local focus caused in this manner have been described:—

I. One form, occurring during ischæmia, consists of isolated action potentials of irregular frequency. It was found possible to follow the frequency up to a rate of 80 per second.

A focus discharging with this type of activity reacts to a passing action potential elicited by shock excitation on the intact part of the nerve with a "silent period," similarly as does the activity from the anterior horn cells. The focus is inhibited just as well as the physiological transmission of impulses are inhibited by antidromic impulses. From this it might be inferred that a physiological and a pathological focus will balance one another: which of them is inhibited depends on their relative frequencies.

II. The second form, seen *after* ischæmia, consists of repetitive dis-

charges occurring in bursts. Each burst is formed of up to 30 impulses with a frequency of 100-180 per second. The individual bursts (grouped discharges) come with low frequency down to 1 per second, and most often regularly.

When the nerve fibre ceased discharging, though the excitability is still high, a passing action potential discharges a burst of spikes. The action potential thus acts as the "trigger" of a trigger zone. This mechanism is easily fatigued.

Stimulation with constant current reactivates the grouped discharges. Submaximal stimulation by a shock applied proximally to the trigger zone in the nerve starts a burst of impulses after some 7 msec., consisting of synchronized discharges gradually damping out. Excitation with higher frequencies than 1 to 5 per second exhausts the trigger mechanism, in which case the burst is cut down from the tail end and the amplitude of impulses diminishes.

An impulse fired antidromically into the trigger zone discharges a burst of impulses which is reflected back in the same nerve fibre and thus is demonstrable in the muscle of the nerve as a pseudo-reflex.

III. These observations from the motor nerve fibres are used in the discussion for explaining certain phenomena characterizing paresthesias.

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PLATE XXXV

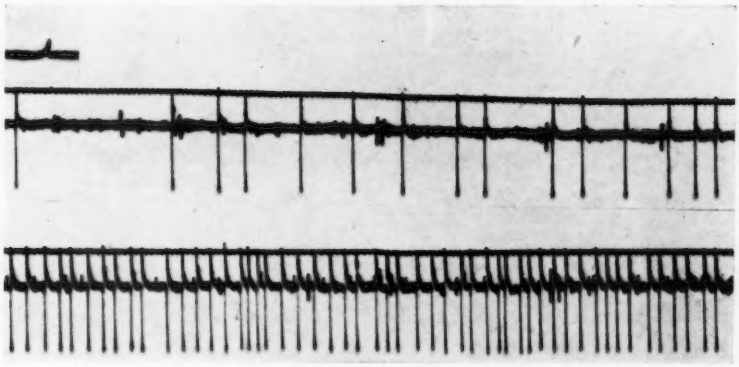


FIG. 1.

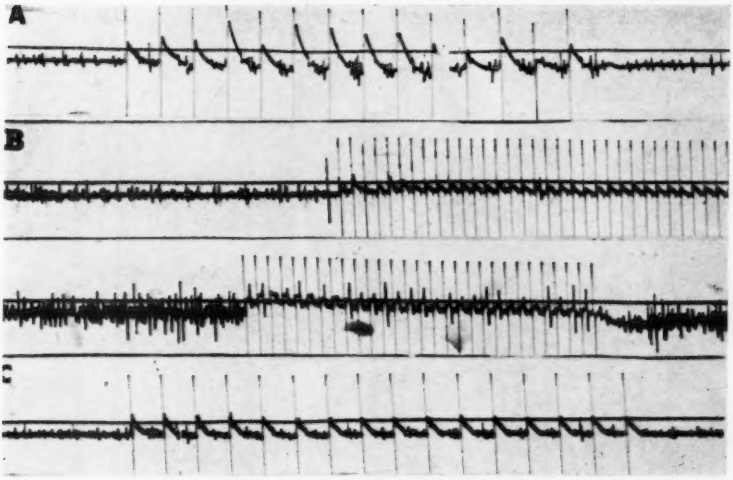


FIG. 2.

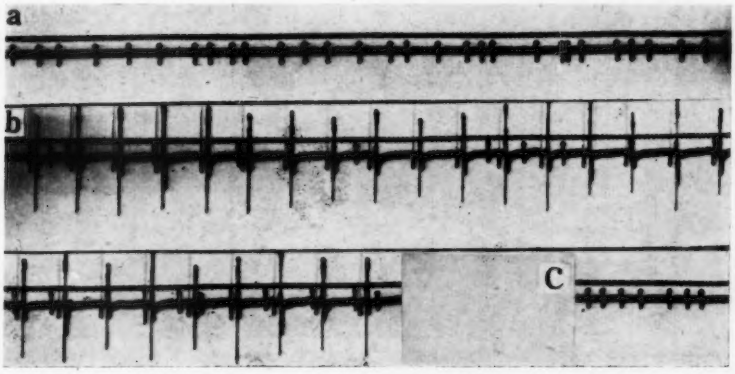


FIG. 3.

To illustrate article by Eric Kugelberg.

PLATE XXXVI

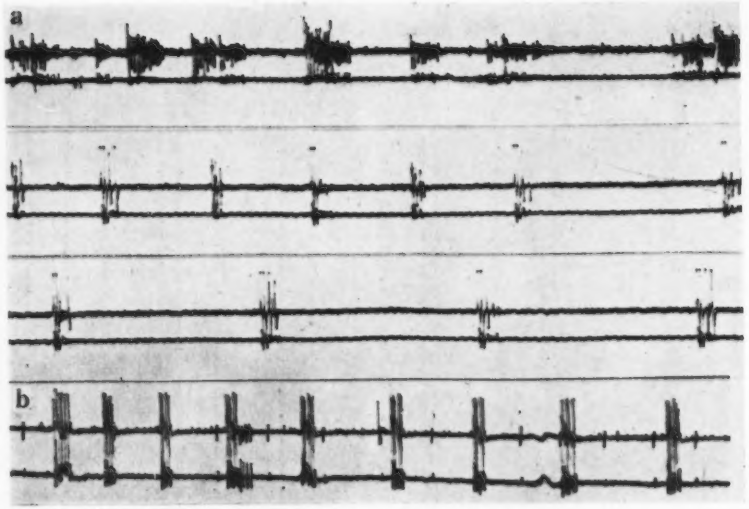
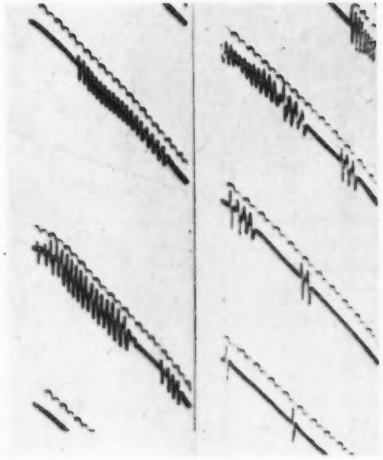


FIG. 4.



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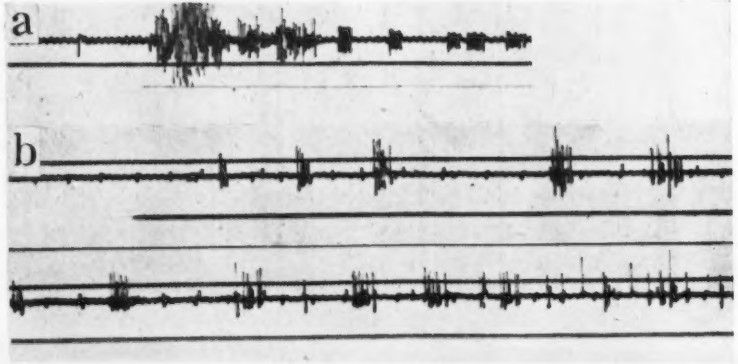

To illustrate article by Eric Kugelberg.

PLATE XXXVII

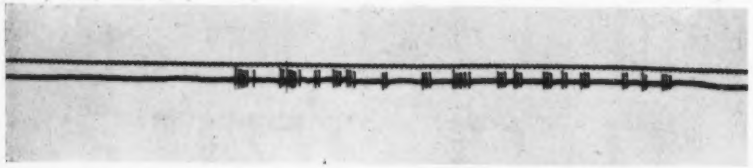

FIG. 7.

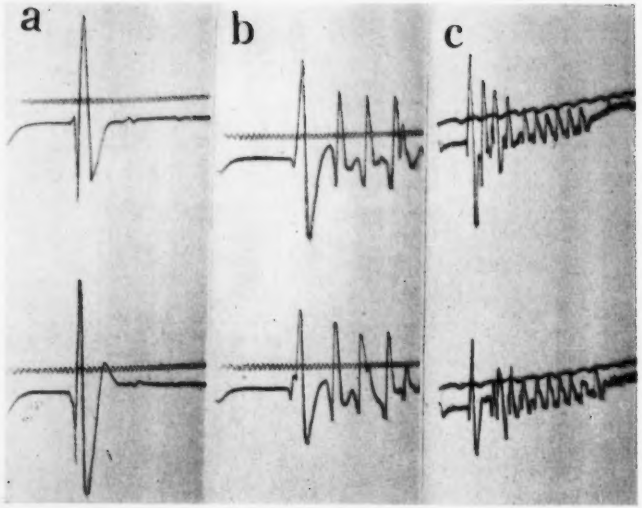

FIG. 8.

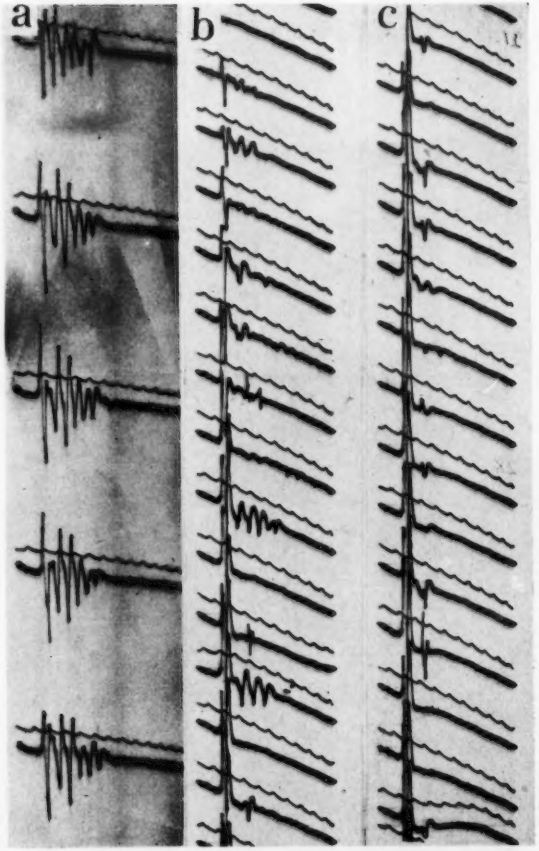

FIG. 9.

To illustrate article by Eric Kugelberg.

PLATE XXXVIII

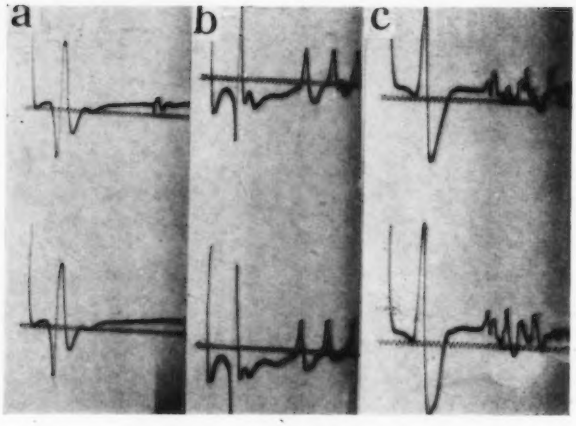

FIG. 10.

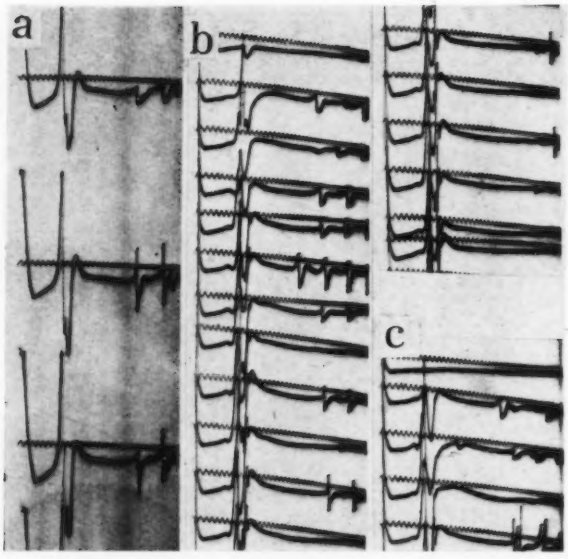

FIG. 11.

To illustrate article by Eric Kugelberg.

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LEGENDS FOR FIGURES (PLATES XXXV to XXXVIII).

FIG. 1—Single action potential discharges during ischæmia. Upper curve at the beginning, lower curve at the culmination of discharges. Time 1/100 sec. Calibration 100 μV.

FIG. 2.—*a* and *b*. The effect of repetitive antidrome volleys elicited by shock stimulation of the ulnar nerve during voluntary contraction. *a*. Stimulation frequency 10 per sec. Shows from the left, action potentials of a slight voluntary contraction. Then follows the large spike belonging to the indirect muscle twitch evoked by the shock, and afterwards the reflex response, here slight or missing succeeded by "a silent period" during which the voluntary innervation is suspended. The voluntary activity then reappears, followed by a new large spike, and so forth. *b*. Stimulation frequency 30 per sec. Upper curve: total suppression of slight voluntary activity, lower curve: ditto of moderate voluntary activity. The small downwards spikes between the large ones are shock artefacts, the other larger intermediate spikes (lower curve) belong to the reflex response elicited by the shock stimulation of muscle afferents and facilitated by the moderate voluntary contraction. *c*. Shows the appearance of the "silent period" in the continuous activity evoked by stimulation with a strong constant current. Shock stimulation frequency 10 per sec. Time 1/100 sec.

FIG. 3.—The effect of shock stimulation on the intact part of the nerve proximally to a spontaneously discharging focus. (*a*) Discharge immediately before the stimulation. (*b*) During the stimulation. (*c*) Immediately after the stimulation. Time 1/100 sec. Full description in text.

FIG. 4.—Grouped discharges from two subjects, led off with two different needle electrodes to two cathode-ray beams from the 1st dorsal interosseus muscle. (*a*) Succession of records showing frequency of a single group gradually declining to 2 per sec. (*b*) Frequency of a single group at start 7 per sec., at termination 4 per sec. Spike amplitude about 200 μV.

FIG. 5.—Records showing the detailed arrangement of the impulses in the grouped discharges Spike amplitude about 200 μV. Time 1/100 sec.

FIG. 6.—The reaction of the trigger zone to passing action potentials induced by a slight voluntary contraction. The dark line below the records indicates that a voluntary contraction is proceeding. Time 1/100 sec. Full description in text.

FIG. 7.—Grouped discharges generated by stimulation of the ulnar nerve after ischæmia with a constant current. Time 1/100 sec.

FIG. 8.—The reaction of the trigger zone to a passing volley elicited by shock stimulation on the intact part of the nerve proximally thereto. (*a*) Before ischæmia, as control. (*b*) After ischemia. The submaximal synchronized spike elicited by the stimulus is followed by a number of spikes gradually damping out. Time 1/1000 sec. (*c*) Same experiment as in (*b*) on a compressed time scale. Time 1/100 sec.

FIG. 9.—The reaction of the trigger zone to repetitive shock stimulation on the intact part of the nerve proximally thereto. (*a*) Stimulation frequency 1 per sec. The synchronized repetitive discharge elicited by the shock shows no tendency to fatigue. The amplitude of the first spike about 2 mV. (*b*) Stimulation frequency, 10 per sec., shows rapid inhibition of the elicited bursts. (*c*) Direct continuation of (*b*). Time 1/100 sec.

FIG. 10.—The reaction of the trigger zone to an antidrome volley elicited by shock stimulation of the ulnar nerve distally thereto. Time in 1/1000 of sec. (*a*) Before ischemia, as control. Shows from the left: shock artefact, action potential belonging to the indirect muscle twitch and then that belonging to a faint reflex response (upper curve). (*b*) After ischæmia. Shock artefact muscle response and a repetitive synchronized pseudoreflex. (*c*) Pseudoreflex in the form of a protracted period of asynchronous activity.

FIG. 11.—The effect of repetitive antidrome volleys in the trigger zone. (*a*) Stimulation frequency 1 per sec., showing no fatigue of pseudoreflex. (*b*) Stimulation frequency 10 per sec., showing rapid inhibition of the pseudoreflex. (*c*) Continuation of stimulation after 20 sec. recovery. Time 1/1000 sec.

ON SIMULTANEOUS BILATERAL STIMULATION OF THE BODY IN A LESION OF THE PARIETAL LOBE.

BY P. W. NATHAN.

(*From a Military Hospital for Head Injuries.*)

It has long been known that a lesion of the parieto-occipital cortex may cause visual inattention. Recently Bender and Furlow (1944) studied the case of a man who had had a gunshot wound of the left parieto-occipital region. This man noticed that when he stared for a sufficient length of time, his vision blurred on the right side; this blurring was not present when he first looked at an object or when he first began to read. It was relieved by resting his eyes, but returned when he concentrated on looking for more than a few minutes. Examination revealed that he was unable to see in the right homonymous field when a concomitant stimulus was applied to the normal field. When he was fixing on a central point he could see an object in the right field: as soon as an object was brought into his left field, the object in the right field could not be seen. This suppression of vision for the right field was not always complete; it fluctuated from a blurring to complete invisibility of an image.

This new and important observation of the suppression of the function of the visual cortex raises the question whether the same phenomenon may occur in lesions of the sensory cortex, the auditory cortex or in the whole of the neopallium. Bender (1945) reported another case in which this phenomenon was found in the realm of cutaneous sensibility.

Another case showing this suppression of tactile sensation is the subject of this report.

Pte. F., aged 36, was hit by a shell fragment on June 27, 1944, in the right posterior parietal region.

On the same evening he was reported to be stuporose, and mildly resistive in behaviour, showing vigorous movements of the right limbs. On the next day he was examined by Captain D. F. Ross, R.A.M.C., who stated that there was probably loss of appreciation of pin-prick on the left side, and that he had a complete left homonymous hemianopia. On the following day he was transferred to this hospital. By then he had regained slight voluntary movements in the left limbs. A radiograph showed metallic foreign bodies to the right of the mid-line in the frontal region. Captain Guthkelch, R.A.M.C., operated on June 29; he found a bone defect 2 in. by ½ in.; pulped brain and numerous bone chips, some at a depth of 4 cm., were sucked out.

By September 2, 1944, there had been some recovery in sensation, so that pinprick could be felt on the left, although sensation was diminished. One month after the injury he had started to walk a little; by September he could walk quite well, but the left upper limb remained in a state of complete flaccid paralysis. All deep reflexes on the left were reported to be diminished.

Two months after wounding he had a psychiatric examination by Major W. R. Reynell, R.A.M.C., who recorded the following results in performance tests. He was tested by Reynell's A and B series (1944), Binet-Simon's mixed sentences, Koh's blocks, a test of cube counting in a perspective drawing, Raven's progressive matrices, the Ray Davis Board, the Babcock sentence, a jigsaw puzzle, and the repetition of digit test. Reynell's tests are designed to detect intellectual loss in adults; they are based on the assumption that certain intellectual abilities or attainments, such as vocabulary, general information, and the power of comprehension, suffer less in deterioration due to organic changes of the brain than do other abilities or attainments, such as the power of reasoning, attention, recent remembering, and the ability to grasp abstract relationships. The tests with Koh's blocks is designed to examine the ability of analysing and synthesizing visually. The Ray Davis board is used to investigate visual memory. In Reynell's tests, the patient scored a difference of 14 in the computed intelligence quotients of the A and B series; this difference is very suggestive of organic intellectual loss. He was able to repeat only 4 digits backwards, and that with difficulty. In the Binet-Simon mixed sentences, his score was that of a normal child of 10. He was unable to do a single pattern with Koh's blocks. In the cube-counting test, he scored 5 out of 15; in this test 10-year-old children score 15 out of 15. He was unable to do the simplest calculations, such as the addition of fourpence and fivepence, the subtraction of six shillings from ten shillings, or 8 from 24, or do the 100—7 test. His Matrix score was 23, placing him below the 5 percentile score for adults, in Raven's Group V (intellectually defective); this is equivalent to a Terman Merrill I.Q. of under 73. When he was re-examined one month later some improvement was found. He could then do the first three patterns with Koh's blocks, but he continued to fail on the Ray Davis board after 6 trials. He could not learn the Babcock sentence after 7 trials. The Matrix result was the same, as was the pictorial representation of cubes test result. He took ten minutes to do a jigsaw puzzle for which the average time was two minutes. To sum up, there was gross intellectual defect, which was likely to be a deterioration; his failure was particularly marked in calculation and in intellectual functions associated with seeing.

His visual field, examined on the Bjerrum screen, showed a slight amount of constriction throughout the left homonymous field, which was maximum in the left lower quadrant.

Eight months after wounding he was re-examined. The visual fields were then normal, except for the slight constriction in the left lower quadrant, more marked in the field of the right eye than that of the left. There was visual disorientation in the left field with a 5 in. error. The left limbs were hypertonic, and he was unable to perform independent finger movements on the left; there was clonus in the left lower limb, and an extensor plantar response. In the left upper limb tactile localization showed an error of 2 in. to 3 in. in the forearm; in neither left limb did he know which digit was being touched; there was complete loss of position sense in the digits on the left, and some impairment in the wrist and elbow.

I first saw the patient on August 14, 1945, fourteen months after wounding. He complained that he found himself useless and that he could not live a normal life, that he had difficulty in finding his way about and in reading and writing, and that he could not use his left hand in a normal manner.

The spacial disorientation affected him in many ways. He found that he lost himself, even in houses that were quite familiar to him. Whenever he came to the roundabout on the road from Oxford to his home in Woodstock, he was disorientated, so that he did not know which road to take (the correct one being straight on); he could not say which road he usually did take, but gave evidence that at least twice he turned to the left; after cycling for about ten minutes along the wrong road he realized his mistake, returned, and again had difficulty at the roundabout in choosing the right road. He stated that on leaving the hospital seven months previously, after being in it six months, he never knew his way about it; nevertheless on returning this time he had remembered the geography of the place. He found that he tended to bump into people and walls on the left, misjudging his distance from them, and that he turned corners before or after he arrived at them. When he went to a public house, he did not know which was his glass when it was put down among the others. He made mistakes in recognizing people, but had no difficulty in picturing or remembering visual aspects of things. He found that when he wrote he could not keep a straight margin, tending to start the next line in the middle of the page; similarly he had difficulty in finding the beginning of the next line when reading. Sometimes in the middle of writing he forgot the shape of a letter. He often made mistakes in dressing himself, putting on his clothes inside out or back to front.

He tended to forget that he had a left hand, and never felt he wanted to use it; although he knew its position, when he used it, he found himself always having to watch it to see where it was going; if he did not take care, he knocked it against things. He stated that it was usually colder than the right in winter, and it was usually blue, but in summer it sweated more than the right one. He said, on questioning, that in his dreams he never used his left hand. He sometimes fell off his bicycle towards the left; then, he never put out his left hand to save himself.

Psychometric examination.—His memory was defective for errands, but rote memory (forward digit retention, learning nursery rhymes) was excellent. His spelling was poor; otherwise his reading and writing were found to be normal, although they were carried out slowly.

In Reynell's A and B series of tests the difference between the two series suggested gross intellectual loss. In the B series, he scored nine in forward digit retention, four in backward; this large difference is indicative of intellectual defect: he was able to do only one of the first eight arithmetical problems. His failure in arithmetic was certainly outstanding from his general intellectual loss.

In the tests for spacial analysis and synthesis with Koh's blocks, he could do only the first two patterns, the time taken being over 75 seconds. When he had eventually done a pattern wrong, he had difficulty in seeing that it was wrong, and greater difficulty in pointing out how it was wrong; he never was able to explain this. With the drawing of cubes in perspective test he scored four out of fifteen.

Routine neurological examination.—After six visits to my room, he remained unable to find his way there on his own.

Cranial nerves: There was partial anosmia on the left; he could differentiate smells on the right, but not on the left. The fundi and discs were normal, and the visual acuity was 6/5 on Snellen's types, J 1 on Jaeger's. The visual field of the left eye was normal, but that of the right showed a little constriction in the left inferior quadrant, a 2 mm. white object at 2,000 mm. being seen at only 20 degrees. When required to touch an object in the left field of vision, using his right hand he made errors of 2 to 5 cm.; and he made the same error in judging the nearer and farther, and the higher and lower of two objects in this field. In judging the nearer and farther of two objects from the fixation point, he was wrong in three

out of twelve trials. In the left lower quadrant he had some difficulty in comparing the relative lengths of two or more objects, making two errors in twelve trials.

In the periphery of the left field, the image of an object was suppressed when objects were held in both visual fields. It was noticeable how this was more marked on some occasions than on others. When the object was retained in the left field it ceased to be seen as soon as the same sized object was presented to the right field; as soon as the object was withdrawn from the right field, the retained object in the left field became visible again When this procedure was reversed, the object being retained in the right field, nothing was seen in the left field when an object was passed into it, and then withdrawn.

His pupils were regular, circular and equal, and reacted normally to light and on accommodation-convergence. External ocular movements were full, except for convergence, which was poorly sustained; he converged to 12 cm., when the right eye diverged; accommodation was 18 cm. for both eyes; Maddox Rod 1°. Stereoscopic vision was fairly good. There was an unsustained nystagmus, more prolonged on looking to the right. The corneal and blink reflexes were normal, as was the jaw-jerk; the muscles supplied by the cranial 5th nerve functioned normally.

On the left side of his face (including all the left side of the chin and the upper neck) there was diminished sensation of light touch with a light camel-hair brush or cotton-wool; pressure sensibility was also diminished. There was complete loss of the sensation of tickle in this area There was a slight but appreciable delay in the sensation of pin-prick and of cold, and the threshold was raised; but when it was passed, these sensations were more vivid than on the normal side. The sensation of warmth was the same on both sides, and there was no delay.

There was moderate left facial weakness of upper motor neurone type.

A forced whisper was heard normally; Rinne's test was positive, and Weber's test showed reference to the left ear; there was slight diminution in bone conduction on both sides. The other cranial nerves were normal.

His gait was normal; when walking, he usually held the left upper limb awkwardly, with the forearm flexed.

There was slight loss of power in the left upper limb, and he could not straighten his flexed fingers; power was normal in the lower limbs. Tone was diminished in the left upper limb, and normal and equal in the lower limbs. There was no tremor. There was atrophy of the pulps of the left digits, which was most marked on the index. All the deep reflexes of the left upper limb were exaggerated; those of the lower limbs were normal and equal. The left superficial abdominal reflexes were diminished. Left plantar stimulation gave an extensor response, with extension and spreading of all the toes.

When his arms were suddenly stretched out before him, the digits on the left became extremely extended, taking up a position reminiscent of that seen in chorea. The left limb tended to sink downwards and outwards; when it was pushed out of its position it over-compensated on return. Finger-nose-finger test showed no intention tremor, but the aim was bad. He could perform rapidly alternating movements if the movements were large enough; he could repeatedly tap the examiner's palm normally, if he was not required to do so too rapidly. All small movements were impossible for the left hand and fingers; in attempting piano-playing movements he did not succeed in moving the digits separately.

The vasomotor and sudomotor state was the same in the two limbs (room temperature 18°C.).

Examining the sensory part of his nervous system it was found that the sense of tickle was absent throughout the left side of the body. Cotton-wool and light touch with a camel-hair brush was described as "less natural" on the left hand and

wrist; it was diminished on the left side of the trunk and in the left lower limb, but was not here "less natural." In the left limbs there were occasional hallucinations of touch; after a succession of light touches, a further one was sometimes felt, although no stimulus was applied. Localization of cotton-wool touch was disturbed (there was slightly more pressure than the term "light touch" would warrant); a touch on the left wrist could not be localized at all, although it was felt; stimuli elsewhere in the upper limb were referred proximally or distally, there being no constant abnormality. Localization was more accurate as the stimulus was moved nearer the trunk, so that it was normal in the upper arm, the trunk and the abdomen. When localization was tested in the left foot and toes there were 2 mistakes in 12 trials. Localization of cotton-wool was similar to that for pin-prick. The sense of light pressure was diminished throughout the left side. Once the blunt end of a pencil pressed into the palm was felt as a needle, seeming both pointed and painful. Usually this blunt stimulus was felt to be much more pointed than on the normal side. The sensations of warm and cold were slightly delayed in the left limbs, the maximum delay being on the left foot; no delay was found on the trunk; the threshold for cold was raised. Sense of vibration was felt for 10 sec. less on the left than on the right upper limb; at points 10 cm. lateral to the umbilicus, it was felt 4 sec. less on the left than the right, and on the pubic crest, 6 sec. less than on the right; in the left lower limb it was felt 10 sec. less than on the right. In testing position sense of the terminal phalanges of the left upper limb he made 7 mistakes in 10 trials; for the digits of the left upper limb he made 6 mistakes out of 10. When required to say which digit was moved on the left hand, he made 5 mistakes out of 10; it was noted that he made no mistakes with the little finger; 8 trials were then made on this finger, and no mistakes were made. When the terminal phalanges of the left toes were tested, he made 5 mistakes in 10 trials; position sense in the rest of the left lower limb was normal. Where position sense was defective movements were always recognized as such, but their direction and extent was not appreciated. He was unable to imitate the position of the left hand and digits with those on the right when his eyes were closed. When figures were written on his skin he was unable to recognize them anywhere; but there was a difference on the two sides; on the right side he thought he was right, but on the left he had no idea what figure was written, and just guessed. Spacial discrimination, tested by the two point test, was greatly disturbed on the left, the disturbance being equal for large and small distances. Throughout the left side, it was found that identical stimuli did not feel identical; later stimuli would be interpreted as lighter; throughout the left, the response bore no quantitative relation to the strength of stimulus.

Examination to Show Suppression of Function of the Damaged Cortex.—All tests were applied according to the following scheme; the numbers used refer to the numbers of this scheme. Left and right refer to the sides of the body. (1) Simultaneous testing of homologous parts on the two sides; (2) the stimulus to the left side was continued, while the stimulus to the right side was applied and removed during the period of stimulation of the left; (3) the stimulus to the right side was continued, while the stimulus to the left side was applied and removed during the period of stimulation of the right.

As far as possible, identical stimuli (except where it is otherwise stated) were used on homologous points on the two sides of the body. The stimuli used were the routine clinical neurological tests of sensation.

Cotton-wool.—Cotton-wool was used, according to the usual practice, as a moving stimulus.

Face: (1) Left not felt. (2) As soon as both sides were stimulated, he felt only

the right; when the right stimulus was removed the left stimulus was felt again, only more faintly than before. (3) Either the left stimulus was not felt when the right was stimulating, or, when the right was stimulating, the left stimulus was not felt to make contact or to be present, but it was felt when it was removed: it was then interpreted as a new stimulus; or, in some experiments, he did feel the left stimulus when it was first applied, but did not feel it remain or be removed.

Using cotton-wool on the face the stimulus on the left had to be lighter than that on the right to be suppressed.

Hands: (1) Left not felt. (2) Suppression of left stimulus throughout. (3) Either the left stimulus was suppressed throughout, or the stimulus on the left was felt only when it was removed, but never when it was applied or was continued. Using cotton-wool on the hands, when the stimulation on the left was sufficiently vigorous, it was never suppressed. But on the fingers no adequate stimulus with cotton-wool could be applied to overcome the suppression; in order to overcome the effect of cotton-wool stimulus on the right fingers, it was necessary to stroke the left fingers with my index.

Antecubital fossæ: (1) Left not felt. (2) Left not felt throughout. (3) Left not felt throughout.

Umbilical region: (1) Left not felt. (2) Left not felt throughout. (3) Left not felt throughout.

Feet: (1) Left not felt. (2) Left not felt throughout. (3) In 6 trials left was not felt throughout, in 4 the stimulus was felt on application and removal only.

Pressure with blunt end of pencil.—The results were similar to those obtained with cotton-wool, but the suppression was less marked.

Face: (1) Both stimuli felt. (2) Both felt in 7 out of 8. (3) Both felt in 6 out of 8.

Hands: (1) In 2 out of 8 both were felt; in 6, the left was suppressed. (2) Left suppressed throughout right stimulation; when right stimulus was removed, the left remained suppressed. (3) Left suppressed, but the removal of the left stimulus was felt.

In order to overcome the suppression of the left stimulus, it was necessary to press the pencil into the pads of the left fingers until the resistance of the bones could be strongly felt; this pressure was firm enough to leave a rim on the skin lasting four minutes.

Feet: (1) Either both felt, or left suppressed. (2) Either left was felt throughout, although "not as blunt as on other foot," or left suppressed throughout. (3) Either left was felt throughout, or the stimulus of the removal of the pencil on the left was felt, and was interpreted as the application of a stimulus.

Deep pain (kneading muscles).—Arms: (1), (2) and (3) No suppression; both felt.

Thighs: (1), (2) and (3) No complete suppression; both felt, but usually the left was felt less than the right.

Vibration sense.—Arms: (1) Left not felt. (2) Left not felt, until right stimulus was removed. (3) Both felt.

Legs: (1) Left felt 10 secs. less than right. (2) Left not felt throughout. (3) Left not felt throughout.

Position sense.—This was so defective on the left that it could not be tested satisfactorily by simultaneous stimulation.

Comment.—Circumstances prevented further work on this case. Enough, however, is presented to show the existence of this phenomenon, and to arouse interest and the search for confirmation in other cases.

It was noted in this case that the sensory adaptation time was reduced on the side of the body controlled by the damaged cortex. In order to interpret the environment it is necessary not only to receive stimuli, but to relate present stimuli to preceding ones, and the absence of present stimuli to the presence of preceding ones. When the sensory adaptation time is reduced, the stimulus is felt for a lesser time than normally; it is of course normal for accommodation and sensory adaptation to occur; but when their duration is abnormal the stimulating environment will not be interpreted in a usual manner. This decrease in the sensory adaptation time results in any stimulus soon ceasing to be felt, so that when a stimulus is removed this is often interpreted as the application of a new stimulus.

It was seen that the removal of a stimulus was more often appreciated than the application of a stimulus. This is doubtless due to the fact that the quantity of stimulus is proportional to the rate of induction of deformation of the receptor, and this rate is faster when a stimulus is removed than when it is applied.

No carefully controlled laboratory tests differentiating the threshold in both cortices were performed. Two points concerning this threshold should be made clear. First, the threshold was not constant, a typical feature of cortical lesions. Secondly, for clinical purposes this phenomenon is so clear that it is unnecessary to work out a threshold to show the difference between the two sides; and it is easy to show that the normal subject has no doubt whatsoever whether he is being stimulated on one or both sides of his body, as soon as the threshold has been passed, and he is able to feel the stimulus.

Although a quantitative investigation might be done, it should be noted that the amount of stimulus necessary to cause the suppression was far from constant. At one time light touch was interpreted as sensation by the damaged cortex, whereas at another time very firm pressure of a very painful stimulus was necessary to overcome the suppression of activity. This feature is what would have been expected in a lesion of the cortex, where it is always impossible to work out a threshold. It would be important to investigate the qualitative aspect of this phenomenon, to find out if one type of stimulus were capable of causing suppression of another; and, if this were so, to work out a hierarchy of sensory stimuli to the cortex. It should also be found out how large an area of the normal cortex inhibits activity of how much of the damaged one: whether stimulation of the normal leg suppresses sensation in the abnormal arm: and even whether stimulation of the normal visual field suppresses sensation in the side of the body with impaired sensation.

The same principle could be used in investigating the influence of the temporal cortex on the vestibular apparatus. Stimulating both labyrinths simultaneously by syringing with water at the same temperature should in the normal give no nystagmus. One might in a case of a damaged cortex expect to find that when this was performed nystagmus to one side might be produced, the function of the damaged cortex being suppressed; it would be of interest to find out to which side this nystagmus would go.

All these questions could be answered if these cases were examined in this matter. It is likely that owing to the presence of battle and air-raid casualties in the country there are many cases showing this phenomenon.

It is illuminating that only a very small change in the technique of clinical examination—testing the two sides of the body simultaneously—was required in order to discover this suppression. This simultaneous testing was first performed by Head and Holmes (1911); they therefore first observed the phenomenon, and reported it in one paragraph in their work on the functions of the sensory cortex, as follows: "A weight is placed in each hand and allowed to remain there. From time to time the patient is asked to estimate the relation between the two weights. He will almost certainly say that the one in the normal hand is heavier; but gradually he begins to think that there is no weight in the abnormal hand, and the sensations produced by its removal may even be mistaken for the reapplication of the weight to the hand." This important observation was not followed up by its authors, and it seems to have remained unnoticed; nor was it known to Bender or myself when our cases were observed.

It was thought at first that this suppression of function of the damaged cortex would be found to be a general law for the entire cerebrum; observation, however, has not borne this out. If the lesion is far forward—affecting the pre- and post-central gyri—no suppression is found. Simultaneous stimuli are felt bilaterally, the one on the affected side having the characteristics of the kind of diminished sensation present with that lesion. This suppression of function of a damaged region may be found to be a characteristic of the parieto-occipital and occipital cortices; the region of cortex or tracts which must be damaged in order to produce it will have to be found out as cases accumulate. In Bender and Furlow's case of suppression of vision in an homonymous field there was also this phenomenon for tactile sensation, as they pointed out in a footnote. There was in addition hemiplegia and global aphasia, which cleared up; there remained acalculia, spelling defect, and dysgraphia. In the case reported here there was hemiplegia, hemianæsthesia, acalulia, and spacial disorientation: the hemiplegia recovered partially and the constriction of

the visual field cleared up to a large extent. This suggests that cases will be found without involvement of the visual fields, and would place the lesion which allows this suppression of sensation in front of the transverse occipital sulcus. It is fortunate that the two cases reported so far had lesions of different hemispheres, thus showing that this is a phenomenon common to both, and not a function of the dominant hemisphere. It is also important to note that both cases showed the phenomenon of unawareness of a limb, one case having a lesion of the dominant hemisphere, the other of the minor hemisphere. It remains to investigate whether all cases of unawareness of a limb or limbs show this suppression, and whether this suppression can exist without this unawareness. If the body schema receives inadequate information about a limb or a half of the body it is reasonable to suppose that this part will tend to drop out of the body schema and also out of the subject's consciousness; therefore it might be expected to find unawareness of a limb as an invariable concomitant of this suppression, although removal of the right hemisphere neither causes unawareness nor anosognosia of the opposite limbs. It is also to be expected that in all cases there will be found a loss of postural sense, for recognition of posture depends on the retention in the plastic model or schema of the preceding positions of the part. If there is suppression of these impressions, although new stimuli may be received, a correct knowledge of the position of the part cannot be obtained. For the condition found on testing is naturally the condition that is present all the time. Testing shows that the damaged cortex is constantly not receiving the normal complement of centripetal impulses, as is the undamaged cortex. When both sides of the body are being equally stimulated by the environment, only one hemisphere is receiving the stimulation adequately. The effect of this on the reacting centrifugal impulses can be imagined. This may account, among other things, for the great degree of inco-ordination and clumsiness seen in such cases in the presence of good position sense and good motor function, when routine neurological tests are performed. This may also bear relation to the vasomotor state of the limbs; for the corticopetal impulses to the damaged cortex being suppressed by the simultaneous stimulation of the normal cortex, the damaged cortex has different information, so to speak, about its side of the body from the other side, and therefore might be expected to react by different vasomotor and sudomotor responses.

It is obvious that this paper contains more questions than answers, and that it presents only a sketch of the phenomenon described. But as circumstances have prevented further investigation of this case and the search

for similar cases at present, and as many others must have opportunities of studying such cases, it seemed justifiable to publish the case as it is, rather than wait until the problem can be more extensively dealt with in a subsequent paper.

SUMMARY.

A case is reported showing the following phenomenon: With a damaged parietal cortex there was appreciation of sensory stimuli when each side of the body was stimulated at different times: when the same stimuli were applied to homologous parts of the body simultaneously, only those going to the undamaged cortex were felt.

The implications of this phenomenon are discussed. Suggestions for its further investigation are put forward.

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On the Contribution of Clinical Study to the Physiology of the Cerebral Motor Cortex. (Victor Horsley Memorial Lecture.) By F. M. R. Walshe. E. and S. Livingstone, Edinburgh, 1947. Price 1s. 6d.

A critical review of the relevant field of experimental physiology, and a brief statement of the nature and value of the clinical contribution to the physiology of the motor cortex, with a plea for a deeper and more consistent conceptual thinking in neurophysiology.

Retinal Structure and Colour Vision. E. N. Willmer. Cambridge University Press. 1946. Pp. 231. 4 colour plates. 72 text figures. Price 21s.

Common experience informs us that the human eye is capable of appreciating two attributes of illumination: its intensity and its colour. The conscious recognition of these two qualities is clearly determined by activities of the cerebral cortex. The initiation of these activities in response to illumination of the eye is equally clearly dependent upon a state of excitation originating in the rods and cones of the retina.

It is possible that some of the available receptors which are covered by the retinal image of an illuminated object will develop activity in response only to one or to the other quality of its illumination, i.e. to a certain degree of intensity or to a certain component of colour.

In his book, Willmer reviews the whole problem of interpreting vision as we know it in terms of such selective receptor stimulation. The review deals with the morphology of the rods and cones, with the chemico-physical changes underlying their excitability, with the electrical changes accompanying activity in the retina and in fibres of the optic nerve, and with the relevant subjective tests of conscious colour-discrimination.

Based upon all these considerations, it sets forth an entirely new theory of colour vision. The conclusions to which the author is led are that recognition of brightness of illumination is primarily, but not exclusively, due to activity of the cones, and that the three sets of receptors, each with a different spectral sensitivity upon which recognition of colours is dependent, are (1) the cones, (2) the commonly recognized dark-adapting rods, here held to be responsible not only for vision at low intensities of illumination, but also for one component of colour vision, and (3) structures, not hitherto recognized, which he calls non-adapting rods dependent for their sensitivity upon some variety of visual purple. Current theories to which these conceptions are opposed hold that brightness estimation is primarily an affair of the cones so long as they are active, that the three receptors necessitated by the trichromatic theory of colour vision are all different types of cone and that the rods are used only for achromatic "moonlight" vision. In direct criticism of these

theories Willmer points out that in the course of natural history the eye has evolved from a type of highly sensitive nocturnally used structure to the dual-purpose eye of man, and that its retina has evolved from one containing exclusively rods, or rods in great excess over cones; it seems to him more natural to suppose that the change in sensitivity of the eye should necessitate a modification of the earlier rod mechanism rather than the development of an entirely new and self-contained system denying photopic sensitivity to the rods and requiring the production of three separate types of cone. Moreover, on grounds of numbers alone, even taking into account this development of the human eye from that of nocturnal ancestors, it would be strange if the eye used only 5 per cent. (cones) of its available receptors for daylight, and kept 95 per cent. (rods) for twilight vision.

Le Gros Clark showed that in the lateral geniculate body of certain primates there are three distinct layers of cells, and suggested that each may correspond with one type of colour receptor. If all these receptors are cones, the chief difficulty of accepting this hypothesis lies in the fact that it does not provide any explanation of what happens to the nerve fibres originating in the odd 130 million rods: this difficulty is removed if it is allowed that the three colour receptors are not all cones but include rods as well. Further, he discusses in detail the grounds for believing that all relevant observations in many different experimental fields are consistent with his view: analysis of the step lengths of the C.I.E. colour chart, of sensations of colour at different light intensities, of the sensation of whiteness, of saturation, of the addition of whiteness to colours and of the effect of mixing of complementary pairs of wave-lengths to give white, all lead him to the conclusion that there is a prima facie case for believing that the phenomena of colour vision can be in great measure accounted for in terms of the activity of rods and cones.

Finally, he states his grounds for postulating the existence of the third, entirely novel, type of receptor. It is claimed that careful re-examination of the retinal elements shows that there are good grounds for regarding the rods and cones of the fovea as being less morphologically distinct than is commonly believed, and for accepting the possibility that there may be a receptor intermediate both in structure and in activity such as his theory requires, i.e. a non-dark-adapting rod dependent for its activity upon some variety of bleached visual purple. He is supported by Wright in his belief that the essential dichromatism of the foveal centre, first reported by Koenig in 1894, has been confirmed, and he suggests that the receptor elements for this are the cones and his non-adapting rods. Over the remainder of the retina full colour vision is provided by these same two elements, with the addition of the ordinary dark-adapting rods which act as modifiers to stamp particular sensations, especially those involving blue, with unique properties rather than to determine new sensations.

This book is clearly unconventional in its outlook and revolutionary in its conclusions. The soundness of the theory advanced can be appraised only by the expert: to the inexpert reader, it is on the whole more easy to follow than the intricacy of its subject-matter might lead one to expect, and the chapter on colour blindness in particular has direct clinical interest.

E. A. B. P.

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